

The Changing Veterinary Pharmaceutical Landscape

Dan Grooms DVM, PhD
Michigan State University
College of Veterinary Medicine

The use of pharmaceutical products in food animals is under close scrutiny by the general public and regulatory agencies around the world. The scrutiny is especially intense with respect to antimicrobial use (antibiotic and antimicrobial are the same thing). Increasing bacterial resistance to antimicrobials and fear of antimicrobial residues in food drives this scrutiny. Either of these situations have potentially life-threatening implications for anyone who might come in contact with a resistant bacteria or chemical residue, so the scrutiny is justifiable. More importantly, they put the dairy industry specifically, and the whole food animal industry in general, at risk for increased scrutiny, increased regulations and ultimately loss of public confidence. Confusion about use of antimicrobials in food animals adds to the scrutiny. Reasons for this confusion that have been postulated include 1) the fact that antimicrobial use in food animals is not a black-and-white issue; it is a complex issue that is frequently over simplified by both critics and proponents, 2) failure to understand that a concern is not equivalent to risk, 3) disconnect between consumers and agriculture, with most consumers being at least three generations removed from the farm and 4) activist messaging - the media and the internet are often inaccurate and misleading regarding antimicrobial use, and in particular antimicrobial resistance and its relationship to use in food-animal production.¹

We can have a healthy debate about the source of antimicrobial resistance and if residues exist; however, the reality is that if we use antimicrobials in food animals, we contribute to the potential risk of antimicrobial resistance developing and antimicrobial residues showing up in human food. It is **IMPERATIVE** that we do everything we can to reduce these risks, while at the same time making sure we properly care for the health of our animals.

Prudent antimicrobial use is the responsibility of everyone involved in the care of food animals. This includes livestock owners, employees, allied industry personnel (e.g. nutritionists) and veterinarians, among others. This message needs to be heard and applied by all of us to take measures towards doing what's right when it comes to responsible use of antimicrobials. No areas of the livestock industry are exempt from the need to use antimicrobials responsibly, as the majority of livestock eventually end up in the human food chain. Whether you run a dairy operation, a heifer raising operation, a feedlot, a cow-calf operation, or raise 4-H steers; how you care for those animals has potential human health impacts. And part of how you care for your animals includes the responsible use of antimicrobials.

By the way, although this discussion revolves around prudent antimicrobial use, the same arguments pertain to any pharmaceutical product used in food producing animals. Anthelmintics, non-steroidal anti-inflammatories, etc. Misuse of any of these drugs has animal health and public health consequences.

The Landscape

Antimicrobial use in food animals is regulated by the U.S. Food and Drug Administration Center for Veterinary Medicine (FDA CVM). However there are many other agencies involved in the oversight of drug use in cattle besides the FDA. These include the Environmental Protection Agency (EPA - approves pesticide labels), the US Department of Agriculture Food Safety and Inspection Service (FSIS - inspects cattle harvest ante- and postmortem and tests for drug residues), United States Department of Agriculture Center for Veterinary Biologics (CVB - vaccine approval), the Drug Enforcement Agency (DEA - defines and enforces regulations related to the distribution and use of controlled substances), individual state veterinary medical boards (define and enforce veterinary practice act), and individual state pharmacy boards (define and enforce pharmacy and drug distribution law).² For dairy operations, there is also the National Conference on Interstate Milk Shipments (NCIMS), which oversees the Pasteurized Milk Ordinance (PMO). The PMO defines procedures for milk sanitation and prevention of milk borne disease.² Regulatory oversight provides assurance in the development of safe products and that no harmful residues enter the food supply.

Efforts have been made to promote the judicious use antimicrobials in animals.^{3,4} These have been largely educational efforts to increase awareness and best practices with respect to prudent drug use in food animals. In 2012, the FDA finalized Guidance for Industry #209⁵ which provides a framework for the voluntary adoption of practices to ensure the appropriate or judicious use of medically important antimicrobial drugs in food-producing animals. This framework includes the principles of phasing in such measures as 1) limiting medically important antimicrobial drugs to uses in food-producing animals that are considered necessary for assuring animal health and 2) limiting such drugs to uses in food-producing animals that include veterinary oversight or consultation. It is apparent that FDA will be introducing policies over time with this framework in mind. Let's examine each of these more carefully.

Principle 1: The use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that are considered necessary for assuring animal health.

FDA believes the use of medically important antimicrobials in food-producing animals for production purposes (e.g., to promote growth or improve feed efficiency) represents an **injudicious** use of these important drugs.⁵ FDA believes that use of medically important antimicrobials for treatment, control, or prevention of specific diseases (disease prevention is defined as administration of an antimicrobial drug to animals, none of which are exhibiting

clinical signs of disease, in a situation where disease is likely to occur if the drug is not administered – see further discussion later), including administration through feed or water, to be a **judicious** use that is necessary for assuring the health of food-producing animals.⁵ The term “medically important antimicrobials” generally refers to antimicrobials that are important for therapeutic use in humans. A list of “medically important antimicrobials” can be found in Appendix A of the FDA Guidance for Industry #152.⁶ As an example and relevant to this proceedings, Table 1 outlines approved antimicrobials in lactating dairy cattle and their status as medically important or not.

Table 1: FDA approved antimicrobials for lactating dairy cattle and their status as medically important. Note: antimicrobials, for the purposes of this table, are defined as those products that have activity against bacteria or parasites.

Antimicrobial	Medically Important?	
	Yes	No
Ceftiofur (Excenel, Excede)	✓	
Penicillin	✓	
Ampicillin (Polyflex)	✓	
Cloxacillin (Dariclox)	✓	
Hetacillin (Hetacin K)	✓	
Oxytetracycline	✓	
Pirlimycin (Pirsue)	✓	
Monensin (Rumensin)		✓
Fenbendazole (Safe-Guard)		✓
Eprinectin (Eprinex)		✓
Moxidectin (Cydectin)		✓

Principle 2: The use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that include veterinary oversight or consultation.

In addition to instituting voluntary measures that would limit use of medically important antimicrobial drugs in food-producing animals to uses that are considered necessary to assure the animals’ health (Principle #1), FDA also believes it is important to phase-in the practice of including veterinary oversight or consultation in the use of these drugs. Essentially what this means is that all antimicrobials considered medically important will eventually fall under the oversight of veterinarians. There are three classes of animal drugs: Over-the-Counter (OTC), Prescription (RX), and Veterinary Feed Directive (VFD). OTC drugs can be sold by any person or establishment without the prescription of a veterinarian. Prescription drugs can only be sold to farmers by a veterinarian or pharmacist, and only with the prescription of a veterinarian. VFD covers drugs intended for use in or on feed, which is limited by an approved application to use under the professional supervision of a licensed veterinarian. Eventually, it is likely that all antimicrobials that are considered medically important will no longer be available OTC.

Examples of this would include injectable penicillin or oxytetracycline, or feed additive antimicrobials such as AS-700.

In 2013, FDA finalized Guidance for Industry #213.⁷ This document essentially implemented the two principles of GFI #209 for feed and water antimicrobials. This document does two things; 1) it eliminated the use medically important antimicrobials for production uses (e.g. growth promotion) and 2) it requires that feed and water antimicrobials must be used under the guidance of licensed veterinarians. Accordingly, in December 2013, the FDA asked pharmaceutical companies to voluntarily phase out the use of medically important antimicrobials in food animals for production purpose. By March 2014, 25 of 26 companies, representing 99.6% of the total sales of medically important antimicrobials used for production purposes, agreed to the FDA's request.⁸ In addition, the vendors intend to remove OTC use of these products in food producing animals and switch to use by veterinary prescription of VFD.

Importantly for the dairy industry, feed would include milk replacers. Therefore this change would affect milk replacers that include medically important antimicrobials (e.g. oxytetracycline). This change would not affect feed additive antimicrobials that are NOT considered medically important (e.g. Rumensin).

The Issue of Disease Prevention⁹

In GFI #209, one of the principles recommended by FDA was to limit the use of medically important antimicrobials in food-producing animals “to those uses that are considered necessary for assuring animal health”. Specifically, production label claims – growth promotion or improved feed efficiency – represented an **injudicious** use of antimicrobials. However, the FDA also recognized in GFI #209 that there are important uses of antimicrobials that are necessary for assuring animal health. Among these uses are the treatment, control and **prevention** of specific diseases. The FDA specifically addresses prevention in GFI #209 and concerns with the appropriateness of these uses. A recent report by the Pew Charitable Trusts¹⁰ has drawn into question the use of antimicrobials for prevention purposes as “judicious”. Therefore, it is important for veterinarians, producers and consumers to understand how antimicrobials are used to **prevent** disease in food animals in a judicious manner. To begin with, it is necessary to define “disease prevention”. Disease prevention uses of antimicrobials occur in situations where disease is likely to occur in a group of animals, but before any of the animals show signs of disease. Obviously, determining important risk factors for when disease is “likely to occur” requires professional judgment; thus, the FDA has deemed prevention uses to be “judicious” when veterinarians are involved and the following factors are considered:

- Prevention is targeted at a specific bacterial agent (e.g. oxytetracycline targeting *Pasteurella multocida* or *Mannheimia haemolytica*)
- There is evidence that the drug will be effective in treating the particular disease (e.g. know effectiveness of the antimicrobial against specific agents)

- The specific preventive use is consistent with accepted veterinary practice
- Preventive use is targeted to animals at risk for developing the specific disease (e.g. weaned dairy calves entering group transition barn)
- No reasonable alternate interventions exist (e.g. no effective vaccines)

GFI #209 also gives examples of what would and would not constitute judicious preventive use of antimicrobials. For example, a veterinarian, based on a client's production practices and health history of that herd, may appropriately authorize antimicrobials for prevention of a specific bacterial disease in cattle experiencing known stressors (transport). Another example given by FDA is the situation where concurrent disease increases the risk of bacterial infection, as is seen when broiler flocks experience *Clostridium perfringens* (necrotic enteritis) in the face of concurrent coccidiosis. On the other hand, FDA would not consider the administration of a drug to apparently healthy animals in the absence of any information that such animals were at risk of a specific disease to be a judicious use. To be considered judicious preventive use, the veterinarian should have: 1) information related to a specific bacterial disease and/or specific risk factors for that particular group of animals and 2) a defined duration of administration (the period of time when the animals are "at risk"). Following these guidelines will assure that veterinarians and producers are using antimicrobials in the most appropriate manner for the particular clinical situation.

Extra Label Drug Use (ELDU)

In short, it is illegal to use drugs in dairy cattle (or in fact all cattle) differently than how they are labeled. However, ELDU can occur under the guidelines laid out by the Animal Medicinal Drug Use Clarification Act (AMDUCA).¹¹ The key to ELDU under AMDUCA is that it must be done under the direction of a licensed veterinarian and a valid Veterinary-Client-Patient- Relationship (VCPR). After that, ELDU can occur as long as specific criteria are met. There are specific instances where ELDU is prohibited. For example, ELDU does not apply to drugs in feed – it is illegal to use drugs in feed (this includes milk replacers) differently than they are labeled – period amen. Some drugs are legal to use in cattle, but are specifically prohibited from being used extra label – for example enrofloxacin (Baytril) is illegal to use in an ELDU manner. Recently, cephalosporins, the most important in the dairy industry being ceftiofur (Excenel, Excede, Spectramast), became severely restricted in ELDU options.¹¹ There are some drugs that are completely illegal to use in food animals - chloramphenicol is a well-known example. A complete list drugs prohibited for use in a an ELDU manner are published in the FDA Code of Federal Regulations Title 21 Part 530.¹³

Compounded Drugs

Compounding of drugs is the customized manipulation of an approved drug(s) by a veterinarian, or by a pharmacist upon the prescription of a veterinarian, to meet the needs of a particular patient. **The use of drugs compounded from bulk ingredients in cattle is currently illegal.** FDA has exercised enforcement discretion when compounding from bulk ingredients in the case of certain poison antidotes. The AVMA policy on compounding in food animals states that compounding is only appropriate in cases of poison antidotes and euthanasia agents where appropriate.^{14, 15} Bottom line, use of compounded drugs in food animal is inappropriate and illegal!!

What Should You Be Doing?

So, as people interested in the safe use of antimicrobials, what can we do to ensure responsible use of antimicrobials? Here are 5 things you can do TODAY to reduce risks of inappropriate antimicrobial use.

1. **Develop a relationship with a veterinarian who will work with you to manage the health of the herd, not just treat sick animals.** This relationship, called the veterinary-client-patient relationship or VCPR, is necessary to obtain most antimicrobials and likely will become more important in the future. The American Association of Bovine Practitioners has established guideline for a VCPR; “Establishing and Maintaining the Veterinarian-Client-Patient Relationship in Bovine Practice”.¹⁶ Key components of a VCPR include; 1) an agreement by both a veterinarian and producer that a VCPR exists, 2) a veterinarian of record with oversight of herd veterinary treatments, 3) clarity of relationships with consultants and other veterinarians, 4) written treatment protocols for all drugs to be used on the farm, 5) written or electronic treatment records, and 6) provision of drugs for only specific time frames and for specific protocols. Outside of future regulatory requirements, this relationship is really important in helping to ensure the health of your animals and the safety of the food they produce.
2. **Use antimicrobials according to their label directions unless specifically directed to use “extra-label” by your veterinarian.** Did you know it is illegal to use antimicrobials in an extra-label manner unless directed by your veterinarian? There is a reason for this. When antimicrobials are used different than their label directions (extra-label or off-label), it can significantly change the time it takes for that drug to clear the animal’s system. When drug residue violations are investigated, one of the most common reasons cited as causing slaughter or milk residues is extra-label use of antimicrobials. Here is an example. The label dose of Procaine Penicillin is 1 cc/100 lbs. with a slaughter withhold time of 14 days. When the dose is doubled or tripled, the recommended slaughter withhold time increases up to 21 days. Important items to find and follow on the label include disease indications, dosage amount and frequency, route of administration (IV,

IM, SQ, orally), storage conditions, drug expiration date, and slaughter withdrawal period. REMEMBER, extra-label use of antimicrobials (or any drug for that matter) in food animals can only be done legally under the direction of a veterinarian. Whereas in the past, producers may have liberally winked at extra-label use and it was not an issue, in today's litigious environment, extra-label drug use is a legal and civil liability that opens the producer up to major consequences.

3. **Keep good records.** Records provide many GOOD things in terms of managing the health, safety, and productivity of our animals. Unfortunately, records are often one of the most neglected management tools. Whether it is to ensure we follow proper withdrawal times or monitoring our treatment success, records are critical for managing the safe use of antimicrobials, as well as the health of our herds. In fact, one of the best ways to keep yourself out of trouble with regulatory agencies (should you ever have a drug residue issue) is to have good records.
4. **Develop appropriate treatment protocols for common health problems.** Protocols help to avoid the "shotgun" approach to treating problems. Protocols should be developed for the most common health problems you face with the assistance of your veterinarian. They should be written down, easily accessible, and reviewed regularly (at least once a year). Protocols should not depend on routine extra-label use where there are alternatives that can be used. For example, talk with your veterinarian about alternatives to Procaine Penicillin that will be effective at the labeled dosage.
5. **Make sure you have a proper diagnosis.** I am going to use a real example to drive home the point of getting a proper diagnosis before giving antimicrobials to animals. Recently, a client had a 900 lb. heifer that suddenly became severely lame on its left rear leg, and was unable to bear any weight. Well, he thought that a good dose of oxytetracycline should fix the problem. Two days later, I get a call as the heifer was not any better. An examination revealed a fractured leg. So, what do you do with a 900 lb., three-legged lame heifer with a broken leg who also has oxytetracycline in its system and 28 days until it can go to slaughter??...BANG! The point is that there are many livestock health issues where antimicrobial therapy is not the treatment of choice. Antimicrobial use in these cases is expensive and increases risk of antimicrobial resistance and residues.

Let's be clear, the livestock industry as a whole has a great track record of providing safe food. However, times keep changing and the demands of not only consumers, but of the public as a whole make it essential that the livestock industry be above reproach in regard to antimicrobial use. That means that what we did yesterday, may not be good enough today. Let's all step forward and take a role in ensuring careful use of antimicrobials. It is in the best interest of the animals we care for and the public who buy our products. **It is the right thing to do.**

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Notes: