Livestock Drug Safety:

Prohibited Drugs
Introduction
Welcome to Prohibited Drugs. This is one in a series of chapters on topics related to food animal drug safety. This chapter will give an overview of drugs prohibited from extralabel use in food producing animals.

This chapter was developed by the Western Institute for Food Safety and Security, or WIFSS, and the UC Davis School of Veterinary Medicine, in partnership with the U.S. Food and Drug Administration (FDA).

Learning Objectives
After reading this chapter, you will be able to:

- Access the most current list of prohibited substances.
- Recognize those drugs and drug uses prohibited by the FDA.
- Explain the reasons why some drugs and drug uses are prohibited in food animals.

Prohibited Drugs
Treatment of food animals with medications has the potential to cause drug residues in the tissue. All drugs have specific directions for use that are provided on the drug label. In some cases, these directions can be modified by a qualified veterinarian, known as extralabel drug use (ELDU). However, there are some compounds that pose a big enough risk to human food safety that any use other than that specified on the drug label is prohibited. This list of FDA prohibited drugs may be found in title 21 of the code of federal regulations part 530.41.

When a medication is prohibited, in general, the reason for prohibition falls under one of three categories. Residues can cause cancer, can cause toxic reactions or can cause antimicrobial resistance.

Cancer-causing Prohibited Drugs
Prohibited drugs that are associated with cancer include diethylstilbestrol (DES), nitroimidazoles, nitrofurans, and sulfonamides.

*Diethylstilbestrol (DES)*
From the 1940s through the 1970s, DES, a synthetic, non-steroidal estrogen, was prescribed to pregnant women for prevention of miscarriage. In 1971, it was shown that daughters born to DES treated mothers had an increased risk of a rare vaginal carcinoma. Consequently, the FDA withdrew use of this drug in pregnant women. During this time, DES was also used in food animal production to promote growth. But because of the proven health risks to people exposed to this drug, in 1979, the use of DES in food animals was prohibited.

Nitroimidazole class

The nitroimidazole family of drugs includes dimetridazole, ipronidazole and metronidazole. Dimetridazole and ipronidazole were originally approved for treatment of blackhead disease in turkeys, a disease caused by parasitic protozoa that affects the liver and cecum. Metronidazole is used in humans for a variety of anaerobic bacterial infections and other parasitic infections. Because this class of compounds has caused tumor production in rodent studies, and because of evidence that associates extralabel use in food animals with potential human health problems, the entire class of compounds is prohibited from use in food animals.

Nitrofuran class

The nitrofuran family includes nitrofurazone and furazolidone. Previously approved for use in poultry and swine to treat a variety of protozoan and other infections, the nitrofuran family of drugs has been associated with tumors in rodent studies, and in 1991 the FDA withdrew approval for systemic animal nitrofuran products. Products are still marketed for topical use in horses, dogs and cats, but use in food animals is prohibited.

Sulfonamide class, “Sulfa” Drugs

In the 1970s and 80s up to 13% of swine and 73% of milk samples contained sulfonamide residues. New regulations have reduced the number of samples containing sulfonamide residues, but these drugs are still one of the most common tissue violations detected by FSIS. Drugs in this class typically begin with the prefix “sulfa” such as sulfamethazine, sulfadimethoxine, and sulfadiazine. Sulfonamides have been associated with increased tumor formation in laboratory rodents.

Because of widespread detection of sulfonamides and its propensity for transference into milk, in 1988, all extralabel use of sulfonamides in lactating dairy cattle over 20 months of age was prohibited.

Sulfadimethoxine is the only currently marketed sulfonamide that is labeled for use in adult dairy cattle. The use of sulfadimethoxine in an extralabel manner, or the use of any other sulfonamide in an adult dairy cow is a violation.
Drugs Prohibited Due to Toxic Reactions

Aside from drugs associated with causing cancer, there are drugs prohibited because of the potential for toxic reactions. They include chloramphenicol, Clenbuterol, and phenylbutazone.

Chloramphenicol

When exposed to chloramphenicol, 1 in 10,000 people will suffer from life-threatening bone marrow suppression. This danger is non-dose related, meaning that trace amounts, even residue levels, may trigger the toxic reaction. Although products are available for dogs and cats, the use of any chloramphenicol product in livestock, including ophthalmic ointments, is prohibited. Chloramphenicol should not be confused with Florfenicol, a closely related drug, which is labeled for use in livestock and not associated with bone marrow suppression.

Clenbuterol

Clenbuterol has a history of being used illegally in livestock to increase weight gain and lean body mass. Toxicity from clenbuterol residues has resulted in the emergency hospitalizations of over a thousand consumers of tainted beef in Spain and France. Although an approved horse product is available, any use in livestock is prohibited.

Phenylbutazone

Phenylbutazone is a potent non-steroidal anti-inflammatory drug approved for horses. In humans, phenylbutazone has been associated with a variety of adverse drug reactions including fatal bone marrow toxicities. After USDA reports of a high incidence of phenylbutazone tissue residues in cull dairy cows, in 2003, CVM prohibited the use of this drug in female dairy cattle older than 20 months of age.

Drugs Prohibited Due to Antimicrobial Resistance

The third reason why some drugs are prohibited is concern that their use in livestock will result in pathogens that are resistant to drugs that are deemed important for treatment of infections in humans,
also known as antimicrobial resistance. These include fluoroquinolones, glycopeptides, cephalosporins, and antiviral medications.

**Fluoroquinolone class**

The fluoroquinolone class is important for treatment of life threatening infections of Salmonella and anthrax. Livestock drugs in the fluoroquinolone class include enrofloxacin and danofloxacin, both of which must be used per label directions. Any deviation from the label directions is prohibited.

**Vancomycin**

Vancomycin is the only glycopeptide marketed in the United States. It is a human approved drug that is used to treat serious bacterial infections and is the last treatment option when other antibiotics won’t work to treat life threatening infections of the bacteria Methicillin-resistant Staphylococcus aureus, or MRSA. With no approved veterinary products, this drug should never be used in food animals.

**Cephalosporin class**

Cephalosporins are an important class of antibiotics used to treat multiple human conditions. Numerous livestock cephalosporin products are available and widely used. In general, cephalosporins must be used per label directions. Exceptions do exist under the supervision of a veterinarian. More details may be found in title 21 of the code of federal regulations part 530.41.

**Antiviral drugs**

Extralabel use of antiviral medications in poultry has resulted in bird flu resistance in other countries. Adamantanes, amantadine and rimantadine, and neuramidases, oseltamivir and zanamivir were prohibited from use in chickens, ducks and turkeys in 2006 by CVM in hopes of curtailling the development of drug resistant influenza in the United States.

**Summary**

There are some drugs that represent enough public health danger that they may only be used on label or not at all if label dosing instructions do not exist. The most current list of these drugs is found in title 21 of the code of federal regulations. If an investigator comes across these compounds, even the presence of these drugs should prompt the investigator to determine whether or not these drugs are being used in an extralabel manner in a food producing species.