UPDATE ON FDA CHANGES FOR DRUG USE IN SHEEP AND GOATS

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Due to concern about increasing antimicrobial drug resistance across all species, the Food and Drug Administration has released new regulations governing antibiotic use in feed for food-producing animals. This presentation reviews regulations currently governing antimicrobial use in sheep and goats, describes Guidance for Industry #209 and #213, and introduces the 2015 Veterinary Feed Directive. The impact of the revised VFD on administration of antimicrobials in feed for sheep and goats is unclear as of July 1, 2016, but the drug use challenges facing veterinarians and small ruminant producers will be discussed.

CURRENT FDA REGULATIONS AFFECTING ANTIMICROBIAL USE IN SHEEP & GOATS

AMDUCA

For many years, veterinarians were able to use any available product for treating animals with little government oversight or regulation. Recognizing that many veterinarians were using drugs in a manner different from the label, the FDA published the final rule for the Animal Medicinal Drug Use Clarification Act of 1994, effective December 9, 1996. AMDUCA allows veterinarians to administer approved animal drugs with New Animal Drug Applications on file for indications and species that are not on the drug label when licensed products are not available, but AMDUCA does not allow administration of drugs in feed.

AMDUCA has differing impact for food and non-food animal veterinarians. Extra-label use of drugs for non-food animals is now acceptable in most situations if it will not pose a threat to human or animal health. These rules allow equine and companion animal veterinarians access to most human drugs as well as all approved animal drugs. Companion animals are rarely consumed for food in this country, so the rules recognize that there is little concern for drug residues in these species. Because the problem of drug residues is of great concern in species consumed for food, AMDUCA regulations for food animals are both restrictive and specific.

AMDUCA outlines what classes of drugs can be used in a manner different from what appears on the label and under what circumstances they can be used. Small ruminant practitioners are frequently asked to prescribe drugs to manipulate reproduction in goats, yet AMDUCA allows extra-label use only to prevent suffering or loss of life. ELDU refers to extra-label drug use or the privilege granted veterinarians to prescribe the use of a legal drug in a manner than is different from what appears on its label. ELDU might mean a different dosage, duration of therapy, method of administration or specie. An important concept is that producers cannot legally use drugs in an extra-label manner, but a veterinarian can prescribe drugs for producers to use in an extra-label manner.
COMPLIANCE POLICY GUIDE 615.115

While medicated feeds may not be administered in an ELDU manner for major species, FDA created an exemption specifically for minor species. As a companion to AMDUCA in 1996, FDA published Guidance for Industry 615.115 that lists the conditions allowing extra-label use of medicated feeds in minor species such as sheep and goats. Within a valid VCPR, a veterinarian may recommend extra-label use of a medicated feed approved for use in a major species based on diagnosis of an active disease for which no other drug treatment is approved. The medicated feed must be for treatment only when the health of the animals is threatened and suffering or death would result from failure to treat the affected animals. Extra-label use of medicated feed is not allowed for production purposes. Once manufactured and labeled as approved for use in a major species, the feed cannot be reformulated to meet the nutritional needs of the intended minor species or relabeled as such. The most common application of CPG 615.115 in small ruminants would be the administration of a higher than approved dose of chlortetracycline in feed prepared for cattle to sheep and goats in order to prevent abortion due to *Campylobacter fetus*.

MINOR USE MINOR SPECIES ACT of 2004

Recognizing that the high cost of obtaining FDA approval for drugs to be used in minor species may exceed potential income for manufacturers, Congress passed the Minor Use Minor Species Act (MUMS) in 2004 to remedy this problem. Pharmaceutical companies provide FDA with dosage, safety and efficacy information for use in minor species of drugs that FDA has already approved for use in a major species.

An important concept is that while MUMS allows extra-label drug use, it does not allow detectable violative residues. Drugs approved for use in a major species such as cattle have legal tolerances established for detectable residues in animal products used for human consumption. While MUMS and AMDUCA allow veterinarians to prescribe drugs approved for use in major species for administration to minor species such as sheep and goats, there are no legal tolerances for any drug residue in animal products from minor species used for human consumption. For example, florfenicol (Nuflor) is labeled for use in beef cattle with a withdrawal period of 28 days for meat but there is a legal tolerance of 0.33 ppm in muscle and 3.7 ppm in liver, and no tolerance for any level in milk. Since florfenicol is not licensed or labeled for use in sheep or goats, there is no legal tolerance for any level of residue in meat or milk. A significant challenge for ELDU in sheep or goats is the need to establish a drug withdrawal period after which there would be no detectible residues in any products for human consumption.

ANTIMICROBIAL DRUGS CURRENTLY APPROVED FOR USE IN SHEEP & GOATS

At this time, both chlortetracycline and neomycin sulfate are approved for use in feed for sheep, and neomycin sulfate is approved for use in feed for goats, but there are specific doses and indications for each use.
Chlortetracycline can be fed to sheep at 10 to 20 grams per ton of feed or 20 to 50 grams per ton of feed for the purpose of improving feed efficiency and rate of gain. However, all antimicrobial drug use in feed for improved rate of gain and efficiency will go away on December 31, 2016. Chlortetracycline can be added to feed to be consumed by sheep at the rate of 10mg/lb./day for treatment of bacterial enteritis caused by *Escherichia coli* and bacterial pneumonia caused by *Pasteurella multocida* susceptible to chlortetracycline. Sheep may be fed this feed continuously for 7 to 14 days with a withdrawal interval of 5 days prior to slaughter. Chlortetracycline can also be added to feed for pregnant ewes at the rate of 80mg/head/day to reduce the incidence of vibronic abortion caused by *Campylobacter fetus* susceptible to chlortetracycline.

Neomycin sulfate can be added to drinking water or milk for both sheep and goats at the rate of 10mg/lb./day for treatment and control of colibacillosis (bacterial enteritis) caused by *Escherichia coli* susceptible to neomycin sulfate. This drug may be administered for up to 14 days with a drug withdrawal interval of 2 days prior to slaughter.

**RECENT FDA CHANGES AFFECTING ANTIMICROBIAL DRUG USE IN FEED**

**GFI #209 AND GFI #213**

In 2012, the Food and Drug Administration announced Guidance for Industry #209 entitled “The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals” which addresses the FDA’s concern over increasing antimicrobial drug resistance. In 2013, FDA released Guidance for Industry #213 which phases out the use of medically important antibiotics administered to food-producing animals in feed and water for growth promotion, and brings them under veterinary control for treatment and disease prevention. The list of medically important antibiotics includes aminoglycosides, cephalosporins, lincosamides, macrolides, penicillins, sulfas and tetracyclines. Pharmaceutical companies have until December 31, 2016 to remove claims for growth promotion and are now transitioning to labels with a prevention or treatment claim and veterinary oversight.

**2015 VETERINARY FEED DIRECTIVE**

On June 2, 2015, the FDA published the revised Veterinary Feed Directive, which affects current VFD drugs and Over the Counter (OTC) antimicrobial drugs that are currently labeled for treatment, prevention and control uses. This change requires major specie livestock producers to obtain a VFD from a veterinarian in order to purchase these antibiotics in feed. Specific regulations detail the duration of the VFD, which animals receive the feed, and record keeping responsibilities. Pharmaceutical manufacturers have until December 31, 2016 to remove all growth promotion claims and transition antimicrobial drugs administered in feed to prevention and treatment claims under veterinary oversight. Antibiotics delivered in water will convert to prescription status, and administration in an extra-label manner will be allowed.

The revised VFD also specifies that the veterinarian and producer must establish a Veterinary-Client-Patient-Relationship that meets the federal VCPR requirements. A list of states whose VCPR rules would be superseded by the federal VCPR can be found at
Three minimum components of the VCPR must be met for the veterinarian to issue a VFD. The veterinarian must assume responsibility for making clinical judgments regarding the health of the animals and the need for medical treatment, and the client must agree to follow the veterinarian’s recommendations. The veterinarian must have sufficient knowledge of the animals in question and this requires that the veterinarian must have visited the premise, examined the animals on the premise, and is aware of the management practices and health status of the animals. Lastly, the veterinarian must be available for follow-up evaluation, or has arranged for emergency care in the event of adverse reaction or treatment failure.

HOW DOES THIS AFFECT SHEEP AND GOATS?

Of major importance to small ruminant veterinarians is that the revised VFD does not allow any extra-label use of antimicrobial drugs administered in feed, so this may lead to dramatic changes in disease prevention or treatment programs for small ruminant producers. The status of CPG 615.115 is in limbo since it was written before the original VFD at a time when antimicrobial drugs were available over the counter in feed. The revised VFD removes all antimicrobial drugs from over the counter availability. The MUMS Act will probably go away because it allows ELDU of antimicrobials in feed and the revised VFD does not allow any ELDU. Discussions with FDA veterinarians indicate no exceptions will be made regarding ELDU under the revised VFD.

The FDA acknowledges the challenges facing small ruminant veterinarians and their producers, and they have stated on several occasions that they are committed to finding a resolution to this problem. As of the CVMA submission date of July 1, 2016, no solution has been announced. Veterinarians and producers working with minor species should work with the FDA to find a solution to the loss of feed administration of antimicrobial drugs in order to protect animal welfare, prevent suffering and loss of life.