**Antimicrobial Stewardship: Impact of New Federal Regulations and Prudent Use Guidelines for Cattle Producers**

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**INTRODUCTION**

One of the primary goals of a cattleman is the production of safe and wholesome beef products for future human consumption. To reach that goal cattle have to remain healthy and producers must utilize good management practices to optimize the health of their herd. Nevertheless, despite our best efforts, bacterial infections do occur and antimicrobials are necessary to protect animal health and welfare. In recent years, antimicrobial use practices in production animal agriculture have come under intense scrutiny and, with this scrutiny, have come new state and federal regulations that will have a dramatic impact on how antimicrobials are used in food producing species. As a result, the United States Food and Drug Administration (FDA) recently published two documents (FDA Guidances for Industry 209 and 213) that detail their views on the judicious use of antimicrobials in food animals and restrict the use of medically-important antimicrobials in feed for the purposes of promoting growth and feed efficiency. The purpose of this document is to provide producers with judicious antimicrobial use strategies that will protect animal health, preserve antimicrobial efficacy by minimizing the development of antimicrobial resistance, and preserve antimicrobial availability.

**FDA GUIDANCE FOR INDUSTRY 209**

Published by the FDA in April 2012, Guidance for Industry 209 represents the FDA’s current thinking on the topic of judicious antimicrobial use in food animals. In this document, the FDA proposed measures to promote more judicious use of antimicrobials in food animals in two ways:

1. Limiting the use of medically important antimicrobials (Table 1) to uses that are considered necessary for assuring animal health and

2. Limiting the use of antimicrobials to uses that require veterinary oversight or consultation.

In other words, the FDA considers the use of antimicrobials for promotion of weight gain and feed efficiency unnecessary and a potential contributor to the increase in the prevalence of antimicrobial resistant bacteria. However, the use of antimicrobials to prevent, treat, or control specific diseases is considered reasonable and necessary for assuring the health of food animals. For example, if it is believed that a group of cattle are at risk of developing respiratory disease because of their history or specific production practices used by a producer, treating this group of cattle with an
antimicrobial approved for prevention of respiratory disease would be reasonable. However, administration of a drug to overtly healthy animals in the absence of specific information suggesting increased risk of disease is not judicious use. Furthermore, the FDA believes that all antimicrobial use, whether the drug is given by injection or administered in the feed or water, should involve the oversight or consultation of a veterinarian. Currently, many of the antimicrobial drugs approved for use in-feed are available over-the-counter. With Guidance for Industry 209, the FDA has suggested that the ability to purchase antimicrobials over-the-counter be phased out and moved to a prescription only or Veterinary Feed Directive (VFD) process. As a result, the FDA has recommended that veterinarians be involved with all decisions regarding antimicrobial use, whether it be treating individual animals or periodic consulting to establish management protocols, to further combat and slow the development of antimicrobial resistant bacteria.

**Table 1.** List of antimicrobial classes considered medically important by the FDA

<table>
<thead>
<tr>
<th>Class</th>
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<tbody>
<tr>
<td>β-lactams (Penicillin, Naxcel, Excenel, Excede)</td>
</tr>
<tr>
<td>Aminoglycosides (Neomycin, AdSpec)</td>
</tr>
<tr>
<td>Macrolides (Draxxin, Micotil, Zactran, Zuprevo, Tylan)</td>
</tr>
<tr>
<td>Phenicols (NuFlor)</td>
</tr>
<tr>
<td>Streptogramins (Virginiamycin)</td>
</tr>
<tr>
<td>Fluoroquinolones (Baytril, Advocin)</td>
</tr>
<tr>
<td>Sulfas (Albon)</td>
</tr>
<tr>
<td>Tetracyclines (LA200)</td>
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**FDA GUIDANCE FOR INDUSTRY 213**

Guidance for Industry 213 was published by the FDA in December 2013 and this document established recommendations for pharmaceutical companies to gradually and voluntarily phase out the use of antimicrobials in feed or water for the promotion of weight gain and feed efficiency. In addition, Guidance for Industry 213 recommended that all use of antimicrobials in feed and water involve the input of a licensed veterinarian. In more basic terms, Guidance for Industry 213 was the implementation of the recommendations contained in Guidance for Industry 209. From the date of passage, the FDA gave the pharmaceutical industry 3 years to adopt these changes and, should compliance be low, further action potentially taken. While this document only provided recommendations and all changes to drug labels were voluntary, all major pharmaceutical companies quickly made changes to their labels to meet the new FDA guidelines.

**IMPLICATIONS OF GUIDANCES 209 AND 213**

Guidances for Industry 209 and 213 clearly laid out the FDA’s position on the in-feed and water use of antimicrobials in food animals for promotion of growth and feed efficiency. As a result of these documents, in-feed and water antimicrobials can no longer be used to promote growth or feed efficiency after January 1, 2017. Therefore, the use of antimicrobials for this purpose would be considered illegal. In addition, any in-feed or water antimicrobial use requires a prescription (water meds) or VFD (feed
meds) order from a veterinarian. Moreover, the veterinarian writing the prescription must be licensed in the state where the animals are housed and have an established veterinary-client-patient relationship (VCPR) with the operation in question before a prescription can be written (see criteria for developing a VCPR below).

RECENT DEVELOPMENTS
More recently, the California State Legislature passed SB 27 and this legislation makes all medically important antimicrobials prescription products. As a result, products such as Procaine Penicillin G, LA 200, Tylan, and Albon will no longer be available over the counter in that state. While this regulation will only affect California it is likely that the Food and Drug Administration will follow suit with similar policies that affect cattle producers nationwide.

VETERINARY FEED DIRECTIVES
A veterinary feed directive (VFD) is a written statement issued by a licensed veterinarian that authorizes the use of a VFD drug or combination VFD drug in or on animal feed. This statement allows a producer to obtain and use animal feed containing a VFD drug to treat animals in accordance with the conditions for use approved by the FDA. A list of antimicrobials that will be affected by the new VFD regulations are listed in table 2 below. It is important to note that this is not an exhaustive list of the products affected by the new VFD regulations and product labels should be consulted prior to use in any food-producing species to ensure all requirements are appropriately met.

Table 2. Antimicrobials affected by VFD regulations

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Names</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlortetracycline</td>
<td>Aureomycin, CLTC, Pennchlor</td>
</tr>
<tr>
<td>Chlortetracycline + Sulfamethazine</td>
<td>Aureo S 700</td>
</tr>
<tr>
<td>Neomycin + Oxytetracycline</td>
<td>Neo-Terramycin, Neo-Oxy</td>
</tr>
<tr>
<td>Oxytetracycline</td>
<td>Terramycin, Pennox</td>
</tr>
<tr>
<td>Tylosin</td>
<td>Tylan</td>
</tr>
<tr>
<td>Tilmicosin</td>
<td>Pulmotil</td>
</tr>
<tr>
<td>Virginiamycin</td>
<td>V-Max</td>
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</tbody>
</table>

Producers should be aware that the VFD guidelines only affect medically important antimicrobials. Antimicrobials and other pharmaceuticals not considered medically important will not be affected by the new guidelines unless they are mixed in an approved combination with a medically important product. Products not affected by VFD guidelines are listed in table 3 below. As stated previously, this is not an exhaustive list of the products affected by the new VFD regulations and product labels should be consulted prior to use in any food-producing species to ensure all requirements are appropriately met.
Table 3. Pharmaceuticals not affected by VFD regulations unless mixed with a medically important drug in an approved combination

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Names</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amprolium</td>
<td>Corid</td>
</tr>
<tr>
<td>Bacitracin</td>
<td>Albac, BMD</td>
</tr>
<tr>
<td>Bambermycin</td>
<td>GainPro</td>
</tr>
<tr>
<td>Decoquinate</td>
<td>Deccox</td>
</tr>
<tr>
<td>Laidlomycin</td>
<td>Cattlyst</td>
</tr>
<tr>
<td>Monensin</td>
<td>Rumensin</td>
</tr>
<tr>
<td>Lasalocid</td>
<td>Bovatec</td>
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WHAT'S THE TAKE AWAY FOR CATTLE PRODUCERS?
The VFD regulations make taking the following steps an absolute necessity:

1. Develop a relationship with a veterinarian that knows their operation (see requirements for formation of a valid VCPR below)

2. Focus on antimicrobial stewardship (see prudent use guidelines below)

3. If the need for feed or water antimicrobials is anticipated, let your veterinarian know so that appropriate steps may be taken to ensure product availability. In some cases, the use of antimicrobials can be avoided if other management practices that have an impact of disease occurrence exist

PRUDENT ANTIMICROBIAL USE GUIDELINES
Implementation of the antimicrobial use guidelines outlined here can help reduce animal pain and suffering, protect the economic livelihood of cattle producers, ensure the continued production of safe and wholesome food, and minimize the development of antimicrobial resistance in important human and cattle pathogens. The following recommendations will help improve antimicrobial use practices on your cattle operations:

1. Focus on disease prevention – The use of vaccines, dewormers, biosecurity, appropriate nutrition, and good husbandry will reduce the incidence of disease and the need for antimicrobials. Herd management protocols should be reviewed regularly and changes made as needed.

2. Diagnose sick animals quickly and accurately – Not all diseases require treatment with an antibiotic. Even when animals have an infection caused by a bacteria there may be other treatment options available that minimize use of antimicrobials on the farm.

3. Select antimicrobials appropriate for the condition being treated – Using veterinary and laboratory advice can help you select drugs that are most appropriate for the diseases encountered on your operation.
4. Keep records – Record animal or group identification, the drug used, date treated, dosage used, route given, and who administered the product. Keep all records and review them regularly.

IMPLEMENTATION OF PRUDENT USE GUIDELINES ON YOUR OPERATION

**Have a Veterinary Client Patient Relationship**

One of the most important principles as it relates to prudent antimicrobial use is developing a working relationship with a veterinarian familiar with your herd, a relationship termed the veterinary client patient relationship (VCPR). To establish a valid VCPR, the following requirements must be met:

a. The veterinarian knows your operation, your management, your cattle, and is involved in diagnosis and treatment. This requires regular and timely visits to the operation in question

b. The veterinarian must be available for follow-up in case of treatment failures

c. A producer is willing to follow a veterinarian’s recommendations for antimicrobial usage

A valid VCPR is not in place if a veterinarian simply writes prescriptions, sells drugs, or makes drugs available to you. Veterinarians that engage in practices such as this are breaking federal law and can jeopardize your livelihood. It is also important to note that a valid VCPR is required by federal law when an antibiotic is used any manner inconsistent with the directions found on the label or if the drug is a prescription product.

**Establish written treatment protocols**

Diagnosis and treatment of most diseases does not need to be done by a practicing veterinarian in many cases. Recognition of many diseases (pinkeye, respiratory disease, footrot) is relatively straightforward and treatment of cattle with these diseases can be done effectively and economically by producers or farm staff. Nevertheless, working with your veterinarian to establish written disease diagnosis and treatment protocols can help simplify decision-making and improve response to treatment. In addition, written protocols provide accountability and determine liability should questions about a treated animal arise. Complete treatment protocols should include a definition of the disease and detailed directions for treatment (drug, dose, route, duration, withdrawals, etc).

**Understand what constitutes extra-label drug use (ELDU)**

Drugs are approved for the treatment of specific diseases in a specific species at a specific dose, route, duration, and frequency of administration. Any use the deviates from what the label allows constitutes ELDU and requires a valid VCPR. ELDU issues are important because approved withdrawal times are based on label directions and any other use may result in violative residues in edible tissues. There are certain drugs that are prohibited from ELDU in food-producing animals and these drugs are as follows:
Examples of illegal ELDU would be the use of Baytril to treat diarrhea in a calf, the use of nitrofurazone puffers to treat pinkeye in cattle, and the use of medicated feeds to prevent pinkeye in cattle.

There are other drug classes that are allowed to be used in an extra-label manner but carry significant restrictions on their use. The class that is most relevant to cattle producers is the cephalosporins (Excenel, Naxcel, Excede) and any use of this class of drugs in ways that deviate from the label dose, route of administration, or duration of therapy is a violation of ELDU policy. For example, the administration of Excede in the muscle of the neck as opposed to the base of the ear is considered illegal. In addition, the administration of Excenel at a dosing rate or dosing frequency higher than what the label allows for longer than the label allows (2 ml/100 lbs once daily for 3-5 days) is illegal.

In addition to ELDU that is clearly illegal due to restrictions placed by regulatory agencies, there are situations where drugs can not be justifiably used in an extra-label manner because the risk of a residue is too great, the use is done purely out of convenience for the person administering the medication, or products labeled for the disease are just as, if not more, effective than the product being used in an extra-label fashion. Examples include the use of Banamine intramuscularly and the injection of penicillin into the membranes of the eye to treat pinkeye.

**Train people who work with livestock on your operation**
People working with livestock must be trained to recognize and treat disease according to established farm protocols. These individuals should have input on the development and implementation of protocols and may provide insight that improves management of different disease conditions. All personnel should be trained using guidelines appropriate for Beef Quality Assurance programs and all protocols should be reviewed regularly with changes made as needed.

**CONCLUSION**
As new federal regulations come into effect and consumer preferences and demand change, cattle producers must be willing to adapt in order to remain competitive. Public pressure is dictating that we change our patterns of antimicrobial use. Producers and veterinarians must be committed to a culture that promotes judicious and appropriate antimicrobial use to minimize the risk of antimicrobial resistance, maintain the long-term effectiveness of antimicrobials currently available, and protect future antimicrobial availability.
VFD FREQUENTLY ASKED QUESTIONS
Multiple questions have arisen since the VFD regulations were passed. Answers to some of the most commonly asked questions are listed below:

1) Veterinarians must send a copy of the VFD order to the feed distributor via hardcopy, fax or other electronic means. If in hardcopy, the order must be sent with the client or directly to the distributor

2) Veterinarians, producers, and feed distributors must retain the VFD order in its original form for 2 years. Medication use records (including mixing records) must also be kept. These MUST be made available to FDA inspectors if requested

3) Expiration dates are the last date that a VFD medication can be fed following the writing of an order by a veterinarian. Some products have expiration dates on the label, others do not. If VFD medication does not specifically list a time for the order to expire, VFD regulations require a veterinarian to limit the VFD order to 180 days or less

4) The difference between an expiration date and duration of use is as follows: expiration dates define the period of time for which the authorization to feed a VFD drug is lawful. The duration of use determines the length of time a VFD drug may be fed to the animals in question

5) The following information must be found on a lawful VFD:
   a. Veterinarian’s name, address, and telephone number
   b. Client’s name, business or home address, and telephone number
   c. Premises at which the animals specified in the VFD are located
   d. Date of VFD issuance
   e. Expiration date of VFD
   f. Name of VFD drug
   g. Species and production class to be fed VFD feed
   h. Approximate number of animals to be fed VFD feed
   i. Indication for which VFD is issued
   j. Level of VFD drug in feed and duration of use
   k. Withdrawal times, special instructions and cautionary statements
   l. Number of refills authorized
   m. Statement: Use of feed containing this VFD drug in a manner other than as directed on the labeling is not permitted
   n. An affirmation of intent for combination VFD drugs
   o. Veterinarians electronic or written signature

6) Additional information may be included on the VFD order but is not required. That information is as follows:
   a. A more specific description of the location of the animals in question (by site, by pen, barn, stall, tank)
   b. Approximate age range of animals
c. Approximate weight range of animals
d. Any other information the veterinarian deems appropriate

7) Feed and water medications MAY NOT be “stockpiled” prior to the VFD regulations going into effect. Any medically important antimicrobials on a producer’s operations MUST have the proper documentation regardless of when they were purchased.

8) Feed and water medications WILL NOT be allowed for use in cattle with footrot or pinkeye. There are currently no products labeled to prevent or treat these conditions and any extra-label use of medications in feed is strictly prohibited. Similarly, there will be no flexibility in how VFD medications are dosed. Label directions MUST be followed in ALL CASES.

9) Veterinarians will have numerous responsibilities under the new VFD regulations and these responsibilities are as follows:

   a. Be licensed to practice in the state where cattle are housed
   b. Operate in the course of professional practice and in compliance with all practice requirements
   c. Write VFD orders in the context of a valid VCPR
   d. Issue VFD orders in compliance and within context of approved drug use
   e. Prepare and sign the VFD order providing all required information
   f. Enter additional discretionary information as necessary
   g. Include all required information necessary when a VFD drug is used in combination with another drug
   h. Restrict or allow combination use of a VFD drug
   i. Provide the feed distributor and client with a copy of the VFD order
   j. Retain the original order for 2 years
   k. Provide VFD orders to inspectors upon request