

Upcoming Changes in Regulations for the Use of Antimicrobials in the Feed and Water of Food Animals with an Emphasis on the Veterinary Feed Directive

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Introduction

There are three routes from which you may expect pressure to be exerted on drug use in food animals: regulatory, legislative, and supply chains. All of these are responsive to public sentiment as well as varying degrees of reliance on sound data. To veterinarians and food animal producers, it sometimes seems like this might be turned into a modified game of rock-paper-scissors, where we wait to see which type of input trumps another as we move from issue to issue. A thought from Dwight D. Eisenhower also comes to mind in relation to all of this input: “it is easy to be a farmer when you are a thousand miles from the cornfield and your plow is a pencil”. If stated today, it might be said as “your plow is a blog”.

It appears that the primary drug issues in veterinary medicine today are (1) antimicrobial drugs and (2) residues, with much of the residue concern also focused on antimicrobials. There are 6 key areas which have garnered much recent attention or which display potential for extremely rapid change in the next 5 years. These areas are (1) the withdrawal of growth promotion uses of antimicrobials, (2) the associated movement of all feed and water uses of antimicrobial drugs in food animals to veterinary feed directive (VFD) or prescription status, (3) potential expansion of antimicrobial use reporting requirements, (4) continued legislative initiatives to remove antimicrobial uses for prevention or control of disease in food animals, (5) use of the AMDUCA regulations as a regulatory tool to attempt to decrease use of targeted drug classes in food animals, and (6) the recent legal activity concerning an FDA/CVM hearing on the hazard status of the use of tetracyclines and penicillins in animal feed.

Guidance for Industry vs. Compliance Policy Guides

There can be confusion as to what is being communicated through Compliance Policy Guides (CPGs) and Guidance for Industry documents (GFIs). Both of these categories may be found under the “Guidance for Industry” heading on the Food and Drug Administration Center for Veterinary Medicine (FDA/CVM) website.¹

An example of a CPG would be CPG Sec. 608.400, Compounding of Drugs for Use in Animals, which can be located by clicking on “Compliance Policy Guides”. This document speaks to FDA concerns about compounding and has guidelines for inspectors as to what types of compounding may be actionable for compliance activities. We, the public, are allowed to see these documents also. This access can provide insight into how the Agency interprets the regulations.

The GFI documents guide industry or other stakeholders in how to comply with requirements for various activities. They are excellent for designing drug approval protocols, but the final protocol should be the subject of a conference with the FDA/CVM prior to conducting the activity. An example of a GFI used in the drug approval process would be VICH GL9, accessed by clicking on the target animal safety or efficacy headings. This document was formerly GFI #85, but the new number reflects that it has gone through the international harmonization process with the European Union and Japan to facilitate the mutual acceptance of clinical data. VICH GL9 guides drug sponsors in application of Good Clinical Practices in the conduct of animal studies.

Neither CPGs nor GFIs are considered binding on the Agency or those with which the Agency is interacting. The agency may use comment periods on proposed CPGs and GFIs as a way to gather input from stakeholders as to the proposed contents.

Key Area 1: Guidance for Industry documents 209 and 213.

Links to the 2 documents discussed herein are available on the FDA Center for Veterinary Medicine website at <http://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm378166.htm>

Guidance 209 – April, 2012

This guidance document puts forth two principles for which the FDA Center for Veterinary Medicine will seek voluntary compliance.

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. This means that any antimicrobial drug listed as medically important for human therapeutics in Appendix A of Guidance 152 will no longer be legal to be used for improvement in feed efficiency or rate of gain after implementation of this guidance. Guidance 209 specifically applies to antimicrobials used in the feed or water for food animals. The FDA states that they feel this principle applies to all antimicrobials used in food animals; however, Guidance 209 does not address over-the-counter injectable antimicrobials such as procaine penicillin G and long-acting 200 mg/ml oxytetracycline products (e.g., Liquamycin LA-200®).

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. This means that the remaining uses of medically important antimicrobials in the feed and water of food animals (prevention, control, and therapy) will require authorization by a veterinarian through a veterinary feed directive. Additives for milk replacer are approved as feed additives, so they are included in this requirement.

The list of medically important antimicrobials in Appendix A of Guidance for Industry #152 includes the following antimicrobial groups with current feed or water use labels (with examples of in-feed or in-water approved antimicrobials). The groups listed may have other drugs that are used in humans, but the examples listed are those used in food animals. These groups will be affected by Guidance documents 209 and 213.

- Aminoglycosides: gentamicin, neomycin
- Lincosamides: lincomycin
- Macrolides: tylosin, tilmicosin (Pulmotil® currently requires a VFD in swine and cattle)
- Penicillins (natural): penicillin G included in combination products
- Streptogramins: virginiamycin
- Sulfonamides: Includes both potentiated (e.g., trimethoprim/sulfa) and non-potentiated sulfonamides. There are no current feed or water potentiated sulfa approvals in the U.S.
- Tetracyclines: chlortetracycline, oxytetracycline, tetracycline

The list of medically important antimicrobials does not include the following antimicrobials with food animal labels. They will not require a VFD or prescription in the future based on Guidance 209, nor will

they lose growth promotion claims on the label, unless added to the list of medically important antimicrobials in the future.

- Ionophores: monensin, lasalocid
- Flavophospholipol: bambarmycins (e.g., Flavomycin[®], Gainpro[®])
- Bacitracin
- Tiamulin

The list of medically important antimicrobials in Guidance 152, Appendix A, includes the following antimicrobial groups for which there are no current food animal feed or water use labels in the United States. Extralabel use in feed is prohibited in the United States. Extralabel use in water is allowed when in conformance with the Animal Medicinal Drug Use Clarification Act (AMDUCA) regulations.

- Penicillins – Penase resistant, antipseudomonal, and aminopenicillin groups
 - Aminopenicillin examples are amoxicillin and ampicillin
- Cephalosporins – first, second, third, fourth generations and cephamycins
 - Ceftiofur is the third generation cephalosporin labeled for use in food animals with injectable and intramammary approvals
 - Cephapirin is the first generation cephalosporin approved for intramammary use in dairy cattle.
 - Cephalosporins are prohibited from any use in food animals which does not conform to the label regimens, meaning that use in water is prohibited since there are no labels including use in water.
- Carbapenems – another beta-lactam group (related to penicillins and cephalosporins) with no veterinary labels
- Monobactams - another beta-lactam group (related to penicillins and cephalosporins) with no veterinary labels
- Quinolones – the forerunner group to the fluoroquinolones, there are no veterinary labels from this group
- Fluoroquinolones – Enrofloxacin was once labeled for water use in poultry but this label was removed by the FDA/CVM in 2005. The sarafloxacin label for water use in poultry was withdrawn by the sponsor in 2000.
 - Enrofloxacin is labeled for injectable treatment and control of respiratory disease in cattle (including dairy heifers less than 20 months of age) and in swine.
 - Danofloxacin is labeled for injectable treatment of respiratory disease in beef cattle.
 - Extralabel use of the fluoroquinolones is prohibited in food animals.
- Glycopeptides – no veterinary labels and prohibited for extralabel use in food animals
- Oxazolidones – no veterinary labels
- Pyrazinamide – no veterinary labels
- Isoniazid – no veterinary labels
- Rifamycins – no veterinary labels
- Chloramphenicol – no food animal labels and prohibited for extralabel use in food animals
- Metronidazole – no veterinary labels and prohibited for extralabel use in food animals
- Polymyxin B – veterinary labels are ophthalmic preparations

A list of affected products, sponsors, and withdrawn products is available on the FDA/CVM website.² There are 283 affected products from 26 sponsors, including new animal drug applications (“pioneer”), abbreviated new animal drug applications (“generic”), and combination new animal drug applications (which can be either pioneer or generic). On March 26, 2014, the FDA/CVM released an update

indicating that 25 of the 26 affected sponsors have indicated they will comply with Guidance Documents 209 and 213.³ This participation accounts for 99.6% of the affected products. All 26 of the sponsors have now committed to participate.

Guidance 213 – December, 2013

Guidance for Industry #213 puts forth nonbinding recommendations for companies to comply with Guidance 209. There was a 3 month period for companies to communicate with the FDA/CVM regarding their intent to comply with the voluntary recommendations in Guidance 209. A 3 year period for companies to comply will expire in December, 2016. After this period, the FDA/CVM would likely take steps against noncomplying sponsors to accomplish these goals through other regulatory routes.

A company may remove the label indications for growth promotion and insert label requirements for veterinary authorization without being subjected to other requirements such as updating the label in other areas (e.g., microbial safety). The guidance document also provides suggested pathways for companies who elect to pursue prevention, control, or therapeutic claims for the regimen previously labeled as a growth promotion claim. The document also makes it clear that generic versions of original proprietary labels must alter their labels to reflect any changes in the original label.

Key Area 2: Veterinary Feed Directive (VFD) final rule – June, 2015

This proposed rule was released in December of 2013 concurrently with the release of the final GFI 213.⁴ A 90 day comment period was established and the FDA/CVM released the final rule on June 2, 2015.⁵ You are referred to the website for the VFD release by the FDA/CVM in order to review a variety of supporting documents, including Guidance for Industry #120, and a fact sheet on the Veterinary Feed Directive and Next Steps.⁶

The final regulation returns to a 2 year record keeping requirement (a one year period was proposed in the draft rule), and the requirement of a Veterinary-Client-Patient relationship in order for a veterinarian to lawfully provide a VFD (the draft rule removed the VCPR and inserted “supervision or oversight). Another change from the previous VFD rule is that the veterinarian keeps the original copy of the VFD.

The definition of a VCPR will be dependent on the state in which the animals reside for which the veterinarian is providing the VFD. If the state does not have a VCPR definition, then the requirements will default to the VCPR basics included in the VFD final rule.

Below is the final VFD rule taken directly from the Federal Register/ Vol 80, No. 106, June 3, 2015/Rules and Regulations, beginning on page 31708 with a detailed response to all comments received on the draft rule. The actual final rule, reproduced by cutting and pasting here, begins on page 31733. Bolded headings are for emphasis here and are not bolded in the Federal Register.

PART 558—NEW ANIMAL DRUGS FOR USE IN ANIMAL FEEDS

3. The authority citation for 21 CFR part 558 is revised to read as follows:
Authority: 21 U.S.C. 354, 360b, 360ccc, 360ccc–1, 371.

4. In § 558.3, revise paragraphs (b)(1)(ii), (b)(6), (b)(7), (b)(9), and (b)(11); and add paragraph (b)(12) to read as follows:

§ 558.3 Definitions and general considerations applicable to this part.

* * * * *

(b) * * *

(1) * * *

(ii) Category II—These drugs require a withdrawal period at the lowest use level for at least one species for which they are approved, or are regulated on a “no-residue” basis or with a zero tolerance because of a carcinogenic concern regardless of whether a withdrawal period is required.

* * * * *

(6) A “veterinary feed directive (VFD) drug” is a drug intended for use in or on animal feed which is limited by an approved application filed pursuant to section 512(b) of the Federal Food, Drug, and Cosmetic Act, a conditionally approved application filed pursuant to section 571 of the Federal Food, Drug, and Cosmetic Act, or an index listing under section 572 of the Federal Food, Drug, and Cosmetic Act to use under the professional supervision of a licensed veterinarian. Use of animal feed bearing or containing a VFD drug must be authorized by a lawful veterinary feed directive.

(7) A “veterinary feed directive” is a written (nonverbal) statement issued by a licensed veterinarian in the course of the veterinarian’s professional practice that orders the use of a VFD drug or combination VFD drug in or on an animal feed. This written statement authorizes the client (the owner of the animal or animals or other caretaker) to obtain and use animal feed bearing or containing a VFD drug or combination VFD drug to treat the client’s animals only in accordance with the conditions for use approved, conditionally approved, or indexed by the Food and Drug Administration.

* * * * *

(9) For the purposes of this part, a “distributor” means any person who distributes a medicated feed containing a VFD drug to another person. Such other person may be another distributor or the client-recipient of a VFD.

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(11) An “acknowledgment letter” is a written (nonverbal) communication provided to a distributor (consignor) from another distributor (consignee). An acknowledgment letter must be provided either in hardcopy or through electronic media and must affirm: (i) That the distributor will not ship such VFD feed to an animal production facility that does not have a VFD, (ii) That the distributor will not ship such VFD feed to another distributor without receiving a similar written acknowledgment letter, and (iii) That the distributor has complied with the distributor notification requirements of § 558.6(c)(5).

(12) A “combination veterinary feed directive (VFD) drug” is a combination new animal drug (as defined in § 514.4(c)(1)(i) of this chapter) intended for use in or on animal feed which is limited by an approved application filed under section 512(b) of the Federal Food, Drug, and Cosmetic Act, a conditionally approved application filed under section 571 of the Federal Food, Drug, and Cosmetic Act, or an index listing under section 572 of the Federal Food, Drug, and Cosmetic Act to use under the professional supervision of a licensed veterinarian, and at least one of the new animal drugs in the combination is a VFD drug. Use of animal feed bearing or containing a combination VFD drug must be authorized by a lawful VFD.

■

5. Revise § 558.6 to read as follows: § 558.6 Veterinary feed directive drugs.

(a) General requirements related to veterinary feed directive (VFD) drugs.

(1) Animal feed bearing or containing a VFD drug or a combination VFD drug (a VFD feed or combination VFD feed) may be fed to animals only by or upon a lawful VFD issued by a licensed veterinarian.

(2) A VFD feed or combination VFD feed must not be fed to animals after the expiration date on the VFD.

(3) Use and labeling of a VFD drug or a combination VFD drug in feed is limited to the approved, conditionally approved, or indexed conditions of use. Use of feed containing this veterinary feed directive (VFD) drug in a manner other than as directed on the labeling (extralabel use) is not permitted.

(4) All involved parties (the veterinarian, the distributor, and the client) must retain a copy of the VFD for 2 years. The veterinarian must retain the original VFD in its original form (electronic or hardcopy). The distributor and client copies may be kept as an electronic copy or hardcopy.

(5) All involved parties must make the VFD and any other records specified in this section available for inspection and copying by FDA upon request.

(6) All labeling and advertising for VFD drugs, combination VFD drugs, and feeds containing VFD drugs or combination VFD drugs must prominently and conspicuously display the following cautionary statement: "Caution: Federal law restricts medicated feed containing this veterinary feed directive (VFD) drug to use by or on the order of a licensed veterinarian."

(b) Responsibilities of the veterinarian issuing the VFD.

(1) In order for a VFD to be lawful, the veterinarian issuing the VFD must:

(i) Be licensed to practice veterinary medicine; and

(ii) Be operating in the course of the veterinarian's professional practice and in compliance with all applicable veterinary licensing and practice requirements, including issuing the VFD in the context of a veterinarian-client-patient relationship (VCPR) as defined by the State. If applicable VCPR requirements as defined by such State do not include the key elements of a valid VCPR as defined in § 530.3(i) of this chapter, the veterinarian must issue the VFD in the context of a valid VCPR as defined in § 530.3(i) of this chapter.

Side Bar, not text from the VFD Rule: 21 CFR Part 530.3(i)

“(i) A *valid veterinarian-client-patient relationship* is one in which:

(1) A veterinarian has assumed the responsibility for making medical judgments regarding the health of (an) animal(s) and the need for medical treatment, and the client (the owner of the animal or animals or other caretaker) has agreed to follow the instructions of the veterinarian;

(2) There is sufficient knowledge of the animal(s) by the veterinarian to initiate at least a general or preliminary diagnosis of the medical condition of the animal(s); and

(3) The practicing veterinarian is readily available for followup in case of adverse reactions or failure of the regimen of therapy. Such a relationship can exist only when the veterinarian has recently seen and is personally acquainted with the keeping and care of the animal(s) by virtue of

examination of the animal(s), and/or by medically appropriate and timely visits to the premises where the animal(s) are kept.”

(2) The veterinarian must only issue a VFD that is in compliance with the conditions for use approved, conditionally approved, or indexed for the VFD drug or combination VFD drug.

Side Bar, not text from the VFD Rule: What is an indexed or a conditionally approved drug?

Indexed drugs: “The Index of Legally Marketed Unapproved New Animal Drugs for Minor Species (the Index) is a list of new animal drugs intended for use in minor species that have had their safety and effectiveness affirmed through an alternative FDA review process. In many cases, minor species drug products are intended for uses that cannot reasonably go through the standard drug approval process. They are often intended for use in species too rare or varied to be used in traditional safety and effectiveness studies. The Index will be especially helpful to individuals treating animals or classes of animals representing markets too small to support the costs of the drug approval process, even with the incentives of the Minor Uses and Minor Species (MUMS) Animal Health Act of 2004.”

Read more about indexed drugs on the FDA/CVM website at the Drug Indexing page on their website.⁷

Conditionally approved drugs: “Only drugs for minor species or minor uses in a major species are eligible for conditional approval. Minor species are all animals that are not major species. A minor use in a major species is the use of a drug in one of the seven major species—horses, dogs, cats, cattle, pigs, turkeys, and chickens—for a condition that occurs: Infrequently and in only a small number of animals each year; or in a limited geographic area and in only a small number of animals each year.

FDA defines a “small number” as fewer than: 50,000 horses; 70,000 dogs; 120,000 cats; 310,000 cattle; 1,450,000 pigs; 14,000,000 turkeys; and 72,000,000 chickens.

For both conditional approval and full approval, the drug company must prove the animal drug to be safe when used according to the label. The difference lies in the effectiveness requirement.

For full approval, the drug company must provide “substantial evidence of effectiveness.” For conditional approval, the drug company has shown the drug to have a “reasonable expectation of effectiveness,” but not yet proven that it meets the “substantial evidence” standard of effectiveness for full approval.”

Read more about conditionally approved drugs on the FDA/CVM website at the Conditional Approval Explained: A Resource for Veterinarians page on their website.⁸

(3) The veterinarian must ensure that the following information is fully and accurately included on the VFD:

- (i) The veterinarian’s name, address, and telephone number;
- (ii) The client’s name, business or home address, and telephone number;

- (iii) The premises at which the animals specified in the VFD are located;
- (iv) The date of VFD issuance;
- (v) The expiration date of the VFD. This date must not extend beyond the expiration date specified in the approval, conditional approval, or index listing, if such date is specified. In cases where the expiration date is not specified in the approval, conditional approval, or index listing, the expiration date of the VFD must not exceed 6 months after the date of issuance;
- (vi) The name of the VFD drug(s);
- (vii) The species and production class of animals to be fed the VFD feed;
- (viii) The approximate number of animals to be fed the VFD feed by the expiration date of the VFD. The approximate number of animals is the potential number of animals of the species and production class identified on the VFD that will be fed the VFD feed or combination VFD feed at the specified premises by the expiration date of the VFD;
- (ix) The indication for which the VFD is issued;
- (x) The level of VFD drug in the VFD feed and duration of use;
- (xi) The withdrawal time, special instructions, and cautionary statements necessary for use of the drug in conformance with the approval;
- (xii) The number of reorders (refills) authorized, if permitted by the drug approval, conditional approval, or index listing. In cases where reorders (refills) are not specified on the labeling for an approved, conditionally approved, or index listed VFD drug, reorders (refills) are not permitted;
- (xiii) The statement: "Use of feed containing this veterinary feed directive (VFD) drug in a manner other than as directed on the labeling (extralabel use) is not permitted.";
- (xiv) An affirmation of intent for combination VFD drugs as described in paragraph (6) of this section; and
- (xv) The veterinarian's electronic or written signature.

(4) The veterinarian may, at his or her discretion, enter the following information on the VFD to more specifically identify the animals authorized to be treated/ fed the VFD feed:

- (i) A more specific description of the location of animals (e.g., by site, pen, barn, stall, tank, or other descriptor that the veterinarian deems appropriate);
- (ii) The approximate age range of the animals;
- (iii) The approximate weight range of the animals; and
- (iv) Any other information the veterinarian deems appropriate to identify the animals specified in the VFD.

(5) For VFDs intended to authorize the use of an approved, conditionally approved, or indexed combination VFD drug that includes more than one VFD drug, the veterinarian must include the drug-specific information required in paragraphs (b)(2)(vi), (ix), (x), and (xi) of this section for each VFD drug in the combination.

(6) The veterinarian may restrict VFD authorization to only include the VFD drug(s) cited on the VFD or may expand such authorization to allow the use of the cited VFD drug(s) along with one or more over-the-counter (OTC) animal drugs in an approved, conditionally approved, or indexed combination VFD drug. The veterinarian must affirm his or her intent regarding combination VFD drugs by including one of the following statements on the VFD:

- (i) "This VFD only authorizes the use of the VFD drug(s) cited in this order and is not intended to authorize the use of such drug(s) in combination with any other animal drugs."
- (ii) "This VFD authorizes the use of the VFD drug(s) cited in this order in the following FDA-approved, conditionally approved, or indexed combination(s) in medicated feed that contains

the VFD drug(s) as a component.” [List specific approved, conditionally approved, or indexed combination medicated feeds following this statement.]

(iii) “This VFD authorizes the use of the VFD drug(s) cited in this order in any FDA-approved, conditionally approved, or indexed combination(s) in medicated feed that contains the VFD drug(s) as a component.”

(7) The veterinarian must issue a written (nonverbal) VFD.

(8) The veterinarian must send a copy of the VFD to the distributor via hardcopy, facsimile (fax), or electronically. If in hardcopy, the veterinarian must send the copy of the VFD to the distributor either directly or through the client.

(9) The veterinarian must provide a copy of the VFD to the client.

(c) Responsibilities of any person who distributes an animal feed containing a VFD drug or a combination VFD drug:

(1) The distributor is permitted to fill a VFD only if the VFD contains all the information required in paragraph (b)(3) of this section.

(2) The distributor is permitted to distribute an animal feed containing a VFD drug or combination VFD drug only if it complies with the terms of the VFD and is manufactured and labeled in conformity with the approved, conditionally approved, or indexed conditions of use for such drug.

(3) The distributor must keep records of the receipt and distribution of all medicated animal feed containing a VFD drug for 2 years.

(4) In addition to other applicable recordkeeping requirements found in this section, if the distributor manufactures the animal feed bearing or containing the VFD drug, the distributor must also keep VFD feed manufacturing records for 1 year in accordance with part 225 of this chapter. Such records must be made available for inspection and copying by FDA upon request.

5) A distributor of animal feed containing a VFD drug must notify FDA prior to the first time it distributes animal feed containing a VFD drug. The notification is required one time per distributor and must include the following information:

- (i) The distributor’s complete name and business address;
- (ii) The distributor’s signature or the signature of the distributor’s authorized agent; and
- (iii) The date the notification was signed.

(6) A distributor must also notify FDA within 30 days of any change in ownership, business name, or business address.

(7) The notifications cited in paragraphs (c)(5) and (c)(6) of this section must be submitted to the Food and Drug Administration, Center for Veterinary Medicine, Division of Animal Feeds (HFV-220), 7519 Standish Pl., Rockville, MD 20855, FAX: 240-453-6882.

(8) A distributor is permitted to distribute a VFD feed to another distributor only if the originating

distributor (consignor) first obtains a written (nonverbal) acknowledgment letter, as defined in § 558.3(b)(11), from the receiving distributor (consignee) before the feed is shipped. Consignor distributors must retain a copy of each consignee distributor's acknowledgment letter for 2 years.

Dated: May 28, 2015.

Leslie Kux,

Associate Commissioner for Policy.

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Key Area 3: Regulatory or legislative initiation of antimicrobial use reporting

Current antimicrobial use reporting in the United States consists of aggregate reporting of drug classes based on sales figures reported to the FDA/CVM by sponsors as required under the Animal Drug User Fee Act (ADUFA) of 2008. In 2013 the FDA/CVM asked for comment on a new form of reporting these sales data, but this proposal did not seem to include more detailed information on actual drug use by species, which is not possible from the aggregate sales data as currently reported.⁹

On May 19, 2015, the FDA/CVM proposed a rule for more detailed reporting under the ADUFA.¹⁰

"The U.S. Food and Drug Administration proposed a rule today that would require animal drug sponsors of all antimicrobials sold or distributed for use in food-producing animals to obtain estimates of sales by major food-producing species (cattle, swine, chickens and turkeys). The additional data would improve understanding of how antimicrobials are sold or distributed for use in major food-producing animals and help the FDA further target its efforts to ensure judicious use of medically important antimicrobials..."

"Consistent with data collection objectives outlined in the Administration's National Strategy for Combating Antibiotic-Resistant Bacteria, this proposed rule is a step toward providing more detailed information to the FDA and the public on changes in antimicrobial sales and distribution over time," said Michael R. Taylor, deputy commissioner for foods and veterinary medicine, FDA. "We plan further actions to complete the task."

Current regulatory authority limits the data collection that FDA can mandate to antimicrobial sales and distribution information. While adding species-specific information will help provide a fuller picture, more detailed information is needed about on-farm use practices to adequately understand links between usage patterns and trends in resistance. The FDA is actively engaged with the U.S. Department of Agriculture, Centers for Disease Control and Prevention, and a wide array of stakeholders to fill this need."

It is quite clear that the next 5-10 years will see use transition to a much more transparent antimicrobial use reporting system for food animals.

Legislative pressure has been applied in an attempt to bring about more detailed reporting. Senator Diane Feinstein put a hold on the Animal Drug User Fee Act (ADUFA) in 2013 as an attempt to force inclusion of increased reporting requirements, which was not successful.

Representative Henry Waxman introduced the "Delivering Antimicrobial Transparency in Animals (DART) Act of 2013" as HR 820 in 2013, which did not make it out of the Subcommittee on Health. This

bill would have required increased reporting of antimicrobial sales for all food animal antimicrobials, and required reporting by end users of antimicrobials in the feed. In 2015, the bill was sponsored by Rep Louise Slaughter (D-NY) as H.R. 2459.¹¹

Key Area 4: Will we see legislative prohibition of the use of antimicrobials for prevention or control of infectious disease?

Bills which purpose to drive the evaluation of prevention and control uses, but which in fact would result in their removal for at least a protracted period of time, continue to be introduced.

Representative Louise Slaughter has again introduced the latest edition of the PAMTA act, “Preservation of Antibiotics for Medical Treatment Act of 2015” (HR 1552).¹² This bill has 39 cosponsors. This bill does not outright prohibit the use of antimicrobials in food animals for anything other than individual animal therapeutic use and non-routine preventive use, but sets a very high bar with a very short timeline to retain their use, clearly with the intention of establishing unattainable requirements.

“(2) WITHDRAWAL.—The Secretary shall withdraw the approval of a nontherapeutic use in food-producing animals of a drug described in paragraph (1) on the date that is 2 years after the date of enactment of this subsection unless—

“(A) before the date that is 2 years after the date of the enactment of this subsection, the Secretary makes a final written determination that the holder of the approved application has demonstrated that there is a reasonable certainty of no harm to human health due to the development of antimicrobial resistance that is attributable in whole or in part to the nontherapeutic use of the drug; or

“(B) before the date specified in subparagraph (A), the Secretary makes a final written determination under this subsection, with respect to a risk analysis of the drug conducted by the Secretary and other relevant information, that there is a reasonable certainty of no harm to human health due to the development of antimicrobial resistance that is attributable in whole or in part to the nontherapeutic use of the drug.”

Representative Slaughter’s definition of “therapeutic” and “non-therapeutic” in the bill is as follows.

“(B) The term ‘therapeutic use’, with respect to a medically important antimicrobial, means the use of antimicrobials for the specific purpose of treating an animal with a documented disease or infection. Such term does not include the continued use of such an antimicrobial in the animal after the disease or infection is resolved.

“(C) The term ‘nontherapeutic use’—

“(i) means administration of antibiotics to an animal through feed and water (or, in poultry hatcheries, through any means) for purposes (such as growth promotion, feed efficiency, weight gain, or disease prevention) other than therapeutic use or nonroutine disease control; and

“(ii) includes any repeated or regular pattern of use of medically important antimicrobials for purposes other than therapeutic use or nonroutine disease control.

“(D) The term ‘noncustomary situation’ does not include normal or standard practice and conditions on the premises that facilitate the transmission of disease.

“(E) The term ‘nonroutine disease control’ means the use of antibiotics on an animal that is not sick but where it can be shown that a particular disease or infection is present, or is likely to occur because of a specific, noncustomary situation, on the premises at the barn, house, pen, or other level at which the animal is kept.”.

On the senate side, Senator Dianne Feinstein (D-CA) has again introduced the “Preventing Antibiotic Resistance Act of 2015” (S 621). This bill has 5 cosponsors and is very similar to PAMTA.¹³

“(i) not later than January 1, 2018, a sponsor of an antimicrobial drug described in paragraph (1) shall submit to the Secretary evidence demonstrating that, with respect to such drug—

“(I) there is evidence of effectiveness in controlling or preventing bacterial disease;

“(II) an approved use is consistent with accepted veterinary practice;

“(III) an approved use is linked to a specific etiologic agent;

“(IV) an approved use is appropriately targeted to animals at risk of developing a specific bacterial disease;

“(V) an approved use has an explicitly defined duration of therapy; and

“(VI) there is reasonable certainty of no harm to human health due to the development of antimicrobial resistance; and

“(ii)(I) if the Secretary determines that the evidence submitted under clause (i) is sufficient to demonstrate that the drug meets the requirements described in subclauses (I) through (VI) of such clause, not later than December 31, 2018, the Secretary shall issue a revised label approval for the antimicrobial drug, as necessary; or

“(II) if the Secretary determines that the evidence submitted under clause (i) is insufficient to demonstrate that the drug meets the requirements described in subclauses (I) through (VI) of such clause, not later than December 31, 2018, the Secretary shall withdraw approval of any indication claims described in paragraph (1)(C) for which the Secretary determines the evidence is insufficient and, as necessary, issue a revised label approval.”

These bills have typically not made it out of committee to the floor, and have been repeatedly introduced over the last decade.

Note on next steps: If you go to the Fact Sheet: Veterinary Feed Directive Final Rule and Next Steps on the FDA/CVM website, you can read some very telling language as to the next initiative to follow GFIs 209 and 213.¹⁴

“The FDA acknowledges the important role medically important antimicrobials play in treating, controlling, and preventing disease in food-producing animals. However, the agency has been actively engaging veterinary organizations, animal producer organizations and other stakeholders to express our position that medically important antibiotics labeled for continuous or undefined durations of use is not consistent with judicious use principles, as outlined in previously-released guidance documents.

In the case of disease prevention, the FDA believes it is important such use is appropriately targeted to animals at risk for a specific disease and the use duration is limited and risk-based...

Long-term or open-ended prevention uses are not covered by the phase-out process for production uses described in Guidance #213. However, the [National Action Plan for Combating Antibiotic-Resistant Bacteria](#) calls for the identification and implementation of measures to foster stewardship of antibiotics in animals. The FDA believes long-term or open-ended use of medically important antibiotics is a significant stewardship issue and intends to seek broad public input on this issue in the summer of 2015.”

It could not be clearer that the next focus of regulatory activity will be continuous feeding of medically important antibiotics for the purpose of disease prevention or control.

Key Area 5: Use of the Animal Medicinal Drug Use Clarification Act (AMDUCA) regulations for regulatory action directed towards a drug class for food animal species

The Cephalosporin ELDU prohibition is an example of a very troubling precedent.¹⁵ The primary concern is that even though there was absolutely no evidence to separate concerns regarding label and extralabel use, the action taken was directed at extralabel use. The use of the Animal Medicinal Drug Use Clarification Act (AMDUCA) AMDUCA regulations as a lower-resistance regulatory pathway is troublesome to those who invested considerable effort in both the AMDUCA and the regulation development process, resulting in legalizing extralabel use in veterinary medicine under specified conditions.

Excerpts from a summary of the cephalosporin extralabel use prohibition are reproduced below from the FDA/CVM website. The source page is entitled Cephalosporin Order of Prohibition Questions and Answers.¹⁶

“FDA’s Center for Veterinary Medicine is issuing an order that prohibits the extralabel use of cephalosporin drugs (not including cephalixin) in cattle, swine, chickens, and turkeys. In its order, FDA is prohibiting what are called “extralabel” or unapproved uses of cephalosporins in cattle, swine, chickens and turkeys, the so-called major species of food-producing animals. Specifically, the prohibited uses include:

- using cephalosporin drugs at unapproved dose levels, frequencies, durations, or routes of administration;

- using cephalosporin drugs in cattle, swine, chickens or turkeys that are not approved for use in that species (e.g., cephalosporin drugs intended for humans or companion animals);
- using cephalosporin drugs for disease prevention.

The following exceptions to the prohibition apply:

- Extralabel use of approved cephalosporin products in food-producing animals;
- Use to treat or control an extralabel disease indication, as long as this use adheres to a labeled dosage regimen (i.e., dose, route, frequency, and duration of administration) approved for that particular species and production class; and
- Extralabel use in food-producing minor species, such as ducks or rabbits.

What are some examples of extralabel uses of cephalosporins that are prohibited by this order?

- In ovo chick injections (injections into chicken eggs) is an unapproved use and is prohibited
- The use of biobullets in beef cattle is an unapproved use and is prohibited
- The extralabel use of human cephalosporin drugs in food-producing major species is an unapproved use and is prohibited
- Prevention uses in food-producing major species are prohibited

What is not prohibited by this order?

- Extralabel use of approved cephalosporin products in food-producing animals;
- Use to treat or control an extralabel disease indication, as long as this use adheres to a labeled dosage regimen (i.e., dose, route, frequency, and duration of administration) approved for that particular species and production class; and
- Extralabel use in food-producing minor species, such as ducks or rabbits”

There is also a concern over species inclusion. Regardless of the lack of evidence to indicate a concern for swine, this species is included in the prohibition. In the evidence cited for cattle, the authors of two of the cited papers state in their discussions that you really can't make the conclusion from the paper for which they were used in the FDA decision, which in the opinion of this author was obvious from reading the articles.^{17,18} The FDA also left out key articles related to cephalosporin use in cattle that were not supportive of their stance on the issue.^{19,20} A published systematic review suggests that the finding of multidrug-resistant bacteria on organic and “conventional” dairies is much more complicated than just comparing antimicrobial use.²¹ The key evidence which really supported the ELDU ban was for the injection of chicken eggs and the resulting change in susceptibility profiles of surviving *Salmonella*. The evidence for concern in cattle was inconsistent, and nonexistent for swine.

There are multiple misperceptions involved in the document. For example, the Agency implies that the label regimen is the best to minimize selection for resistance. In fact, there is absolutely no evidence to support this claim. The label regimen is developed based on efficacy, not on suppression of resistance selection. We have very little evidence to support optimal duration of antimicrobials for therapy, let alone the relationship of duration and magnitude of exposure to the potential for selection of resistant organisms during therapeutic protocols.

The prohibition allows the use of ceftiofur for extralabel indications but not with an extralabel regimen. The result of having the ability to use an antimicrobial for off-label indications but not the ability to adjust the dosage appropriately is completely nonsensical, and is likely to contribute to selection for antimicrobial resistance.

The most telling direct quote from the order of prohibition was from the section refuting the allegation that the FDA/CVM was relying on the precautionary principle. *“In the preamble to the final rule, FDA addressed the question of what type of evidence would be necessary by saying that the risk determinations that would lead to prohibition of an extralabel use typically will involve documented scientific information. However, the Agency believes that it is not limited to making risk determinations based solely on documented scientific information, but may use other suitable information as appropriate.”*

While the current FDA/CVM leadership is committed to prevention and control uses being classified as judicious therapeutic uses of medically important antimicrobials, future leadership may not share this view. The precedent of the evidence standards in the cephalosporin ELDU prohibition are troublesome.

Key Area 6: Hearings on whether the uses of penicillins and tetracyclines in animal feed are a hazard to human health.

In 2011, The National Resources Defense Council (NRDC), the Center for Science in the Public Interest, Food Animal Concerns Trust, and the Union of Concerned Scientists, filed a lawsuit against the FDA/CVM in the U.S. District Court for the Southern District of New York.²² This lawsuit sought to force the FDA/CVM to act on the 1977 Notice of Opportunity for a Hearing (NOOH) which sought to address the use of tetracyclines and penicillins in animal feed. On March 22, 2012, the magistrate judge ruled that the U.S. Food and Drug Administration must act on the 1977 NOOH regarding in-feed use of tetracyclines and penicillins in animal feeds.²³ (The FDA/CVM had withdrawn this NOOH in December of 2011, as published in the December 22, 2011 Federal Register.²⁴) The FDA Commissioner (Margaret Hamburg), Secretary of Health and Human Services (Kathleen Sebelius), and Director of the FDA/CVM (Bernadette Dunham) appealed this decision in the United States Court of Appeals, Second Circuit, on May 21, 2012.²⁵

The history leading up to the NOOH and subsequent activities of the FDA/CVM on this issue were detailed in a presentation by two FDA/CVM representatives at a the symposium “Public Health Implications of the Use of Antibiotics in Animal Agriculture” held as part of the Annual Meeting of the American Society of Animal Science in August of 1985.²⁶ In 1981, the FDA/CVM was instructed by the house appropriations committee to hold in abeyance any implementation of the proposed withdrawals pending the results of studies to evaluate the relationship of feed use of these antimicrobials to human health.

The NRDC has previously filed a petition with the secretary of Health and Human Services to declare the subtherapeutic use of penicillin and the tetracyclines in animal feeds an imminent hazard to the public health (Nov 20, 1984). The FDA/CVM held a “legislative type” hearing on January 25, 1985 to evaluate the evidence. If the Secretary would have found the use of these antimicrobials to be an imminent hazard to public health, a formal evidentiary public hearing before an administrative law judge would have been required for removal of these uses.

Back to today, on July 24th, 2014, the United States Court of Appeals for the Second Circuit released a ruling on the appeal in which they reversed the decision and stated that the FDA was not required to hold the hearings. It remains to be seen whether an appeal of this ruling will be filed.

Summary

The sum of these 6 key areas reflect the consistent upheaval in drug use in food animals. The issue of growth promotion use of medically important antimicrobial drugs is largely settled in the United States, but the issue of prevention and control uses is just gaining momentum. This issue, as well as how veterinarians will accomplish the increased requirements for veterinary authorization of feed and water antimicrobial drug use, will demand a lot of attention in the near future.

¹ Guidance for Industry. U.S. Food and Drug Administration Center for Veterinary Medicine. Accessed 7-28-2014 at <http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/default.htm>.

² List of Affected Products. Food and Drug Administration Center for Veterinary Medicine Website. Accessed 4/1/2014 at <http://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/JudiciousUseofAntimicrobials/ucm390429.htm>.

³ FDA Update on Animal Pharmaceutical Industry Response to Guidance #213. March 26, 2014. Accessed 4/1/2014 at <http://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/JudiciousUseofAntimicrobials/ucm390738.htm>.

⁴ FDA Takes Significant Steps to Address Antimicrobial Resistance. Accessed 7-28-2014 at <http://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm378166.htm>.

⁵ Department of Health and Human Services Food and Drug Administration. 21 CFR Parts 514 and 558 [Docket No. FDA-2010-N-0155] Veterinary Feed Directive Agency: Food and Drug Administration HHS. Action: Final rule. Federal Register/Vol. 80, NO. 106/ Wednesday, June 3, 2015/ Rules and Regulations.

⁶ CVM Updates. FDA Regulations to Help Ensure Judicious Use of Antibiotics in Food-Producing Animals. Accessed 7-11-2015 at <http://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm448620.htm>.

⁷ Food and Drug Administration Center for Veterinary Medicine, Minor Species, Drug Indexing. Accessed 7-17-2015 at <http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/MinorUseMinorSpecies/ucm070206.htm>.

⁸ Food and Drug Administration Center for Veterinary Medicine, Resources for You, Conditional Approval Explained: A Resource for Veterinarians. Accessed 7-17-2017 at <http://www.fda.gov/animalveterinary/resourcesforyou/ucm413948.htm>.

⁹ FDA Proposes Revision to Annual Report on Antimicrobials for Food-Producing Animals. Accessed 10-15-2013 at <http://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm369758.htm>.

¹⁰ FDA News Release. FDA proposes rule to collect antimicrobial sales and distribution data by animal species. Accessed 7/12/2015 at <http://www.fda.gov/newsevents/newsroom/pre ssannouncements/ucm447244.htm>.

¹¹ H.R. 2459 114th Congress, 1st session. Accessed 7/12/2015 at <https://www.congress.gov/bill/114th-congress/house-bill/2459/text>.

¹² Preservation of Antibiotics for Medical Treatment Act of 2015. Accessed 7/12/2015 at <https://www.congress.gov/bill/114th-congress/house-bill/1552>.

¹³ Preventing Antibiotic Resistance Act of 2015. Accessed 7/12/2015 at <https://www.congress.gov/bill/114th-congress/senate-bill/621>.

¹⁴ FDA/CVM FACT SHEET: Veterinary Feed Directive Final Rule and Next Steps. Accessed 7/12/2015 at <http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/ucm449019.htm>.

¹⁵ New Animal Drugs; Cephalosporin Drugs; Extralabel Animal Drug Use; Order of Prohibition. 21 CFR Part 530. Final rule. Accessed 10/15/2013 at <http://www.gpo.gov/fdsys/pkg/FR-2012-01-06/pdf/2012-35.pdf>.

¹⁶ Food and Drug Administration Center for Veterinary Medicine. Cephalosporin Order of Prohibition Questions and Answers. Accessed 9-21-2015 at <http://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/ucm421538.htm>

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- ¹⁷ Berge AC, Moore DA, Sischo WM. Prevalence and antimicrobial resistance patterns of *Salmonella enterica* in preweaned calves from dairies and calf ranches. *Am J Vet Res* 67:1580-1588, 2006.
- ¹⁸ Warnick LD, Kanistanon PL, McDonough LP. Effect of previous antimicrobial treatment on fecal shedding of *Salmonella enterica* subsp. *enterica* serogroup B in New York dairy herds with recent clinical salmonellosis. *Prev Vet Med* 56:285-297, 2003.
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- ²⁰ Daniels JB, Call DR, Hancock D, et al. Role of ceftiofur in selection and dissemination of bla-CMY-2 mediated cephalosporin resistance in *Salmonella enterica* and commensal *Escherichia coli* isolates from cattle. *Appl Environ Microbiol* 75:3648-3655, 2009.
- ²¹ Wilhelm B, Rajic A, Waddell L, et al. Prevalence of zoonotic or potentially zoonotic bacteria, antimicrobial resistance, and somatic cell counts in organic dairy production: current knowledge and research gaps. *Foodborne Pathog Dis* 6:525-539, 2009.
- ²² Consumers groups sue FDA's Center for Veterinary Medicine over subtherapeutic uses of antibiotics. *DVM* 350. June 1, 2011. Accessed 10/16/2013 at <http://veterinarynews.dvm360.com/dvm/Veterinary+Food+Animal/Consumer-groups-sue-FDA's-Center-for-Veterinary-Med/ArticleStandard/Article/detail/725023>.
- ²³ Judge to FDA: Revive Proposal to Restrict Animal Antibiotics. Gretchen Goetz in *Food Safety News*, March 24, 2012. Accessed 10/16/2013 at <http://www.foodsafetynews.com/2012/03/judge-to-fda-revive-proposal-to-restrict-animal-antibiotics/#.UI5qP1MwLa9>.
- ²⁴ Withdrawal of Notices of Opportunity for a Hearing; Penicillin and Tetracycline in Animal Feed. *Federal Register* 76(246), pp. 79697-79701, 2011.
- ²⁵ FDA Appeals Mandate to Ban Three Animal Antibiotics. *News Desk*, *Food Safety News*, June 1, 2012. Accessed 10/16/2012 at <http://www.foodsafetynews.com/2012/06/fda-appeals-mandate-to-ban-three-animal-antibiotics/#.UI5q-VMwLa->.
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