

Regulations Today: Wading through VFDs, VCPRs, Prescriptions, ELDU Prohibitions, Proposed and Final Rules, and Guidance Documents.

Michael D. Apley, DVM, PhD, DACVCP

Department of Clinical Sciences, Kansas State University, Manhattan, KS, 66506

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 antimicrobial drugs and 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 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: bambermycins (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) proposed regulation – December, 2013

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 is still gathering input through stakeholder meetings and other activities.

This proposed regulation has 5 key changes in the existing VFD regulation

- User friendly reorganization of the VFD rule
- Increased flexibility for licensed veterinarians issuing VFDs
 - The current regulation requires veterinary “supervision” for a VFD to be written. The proposed regulation changes this to “supervision or oversight”.
 - The proposed regulation removes the explicit veterinary-client-patient relationship (VCPR) provision and replaces it with the requirement that veterinarians ordering the use of VFD drugs must be “in compliance with all applicable veterinary licensing and practicing requirements”. This defers the VCPR standard to the veterinary profession and the individual states to determine the requirements of a valid VCPR.
 - The veterinarian will be required to specify duration of use, approximate number of animals to be fed the medicated feed, and level of VFD drug in the feed. However, they will not be required to specify the amount of medicated feed to be dispensed.
- Continued access to Category I type A medicated feed articles by unlicensed feed mills
 - Currently, a VFD drug is automatically a Category II medicated feed, which means that the type A feed article for that drug would only be available to the limited number of licensed feed mills. The proposed regulation would not require a VFD drug to automatically become a Category II medicated feed.
- Increased flexibility for animal producers purchasing VFD feeds
- Lower record keeping burden for all involved parties
 - Duration of record keeping is proposed to be dropped from 2 years to 1 year

Discussions related to how veterinarians will provide all of these new VFDs as well as the requirements for a valid relationship between producer and veterinarian are taking place at the state level. The FDA/CVM made it clear in GFI #120 that “The term “appropriately licensed” veterinarian, as it pertains to 21 CFR 558.6, means that the veterinarian has a valid license to practice veterinary medicine in the State in which the animals being treated are located”.⁵

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. The FDA/CVM has recently asked for comment on a new form of reporting these sales data, but this proposal does 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.⁶

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 has introduced the “Delivering Antimicrobial Transparency in Animals (DART) Act of 2013” as HR 820. As of 3/1/2013 it had been referred to the Subcommittee on Health.⁷ This bill would require increased reporting of antimicrobial sales for all food animal antimicrobials, and requires reporting by end users of antimicrobials in the feed. A check on this bill through Thomas.gov revealed no further activity as of 7/28/2014.

The FDA/CVM has recently asked for input on how increased antimicrobial use data might be collected for food animal uses. This input has been collected and the FDA/CVM is considering how additional antimicrobial use information might be collected. The direction and the ultimate endpoint of all of these activities remains unknown at present.

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 2013” (HR 1150).⁸ This bill has 55 cosponsors and as of 7/28/2014 has been referred to the House Subcommittee on Health. This bill does not outright prohibit the use of antimicrobials in food animals for anything other than individual 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 benchmarks.

On the senate side, Senator Dianne Feinstein has introduced the “Preventing Antibiotic Resistance Act of 2013” (S 1256). This bill has 12 cosponsors and is very similar to PAMTA.⁹ As of 7/28/2014, it has been referred to the Senate Committee on Health, Education, Labor, and Pensions.

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

Key Area 5: Use of the 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.¹⁰ 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.

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.^{11,12} The FDA also left out key articles related to cephalosporin use in cattle that were not supportive of their stance on the issue.^{13,14} 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.¹⁵ 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.¹⁶ 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.¹⁷ (The FDA/CVM had withdrawn this NOOH in December of 2011, as published in the December 22, 2011 Federal Register.¹⁸) 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, 2012.¹⁹

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 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 1985.²⁰ 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>.

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- ⁵ Guidance for Industry - Veterinary Feed Directive Regulation Questions and Answers Final Guidance. March 26, 2009. Accessed 7-28-2014 at <http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052660.pdf>.
- ⁶ 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>.
- ⁷ Delivering Antimicrobial Transparency in Animals Act of 2013. Accessed 10/15/2013 at <http://thomas.loc.gov/cgi-bin/bdquery/D?d113:1:./temp/~bdwT7y:./bss/>.
- ⁸ Preservation of Antibiotics for Medical Treatment Act of 2013. Accessed 10/15/2013 at <http://thomas.loc.gov/cgi-bin/bdquery/D?d113:3:./temp/~bd3tNp:@@L&summ2=m&./bss/>.
- ⁹ Preventing Antibiotic Resistance Act of 2013. Accessed 10/15/2013 at <http://thomas.loc.gov/cgi-bin/bdquery/D?d113:37:./temp/~bdl8tC:./bss/>.
- ¹⁰ 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>.
- ¹¹ Berge AC, Moore DA, Sisco 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.
- ¹² 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.
- ¹³ Heider LC, Funk JA, Hoet AE, et al. Identification of *Escherichia coli* and *Salmonella enterica* organisms with reduced susceptibility to ceftriaxone from fecal samples of cows in dairy herds. *Am J Vet Res* 70:389-993, 2009.
- ¹⁴ 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.
- ¹⁵ 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.
- ¹⁶ 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>.
- ¹⁷ 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>.
- ¹⁸ Withdrawal of Notices of Opportunity for a Hearing; Penicillin and Tetracycline in Animal Feed. *Federal Register* 76(246), pp. 79697-79701, 2011.
- ¹⁹ 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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