DAIRY VETERINARY NEWSLETTER

November 2019

FDA Plans to End OTC Sales of Medically Important Antibiotics for Animal Treatment

Increased regulation of antimicrobial use in animals is a trend in many of the developed countries in the world, and the U.S. is following suit. On September 23, 2019 the FDA released draft guidance for industry (GFI) #263, a 13-page document, for comment. The comment period ends 12/24/19. Following in the wake of earlier GFI documents released over the past 7 years, this is intended to build upon the Veterinary Feed Directive (VFD) that regulates most medicated feed for animals, birds, fish and bees. The entire GFI 263 can be found at: https://www.fda.gov/media/130610/download

The introduction to GFI 263 states: "This guidance is intended for - - animal drugs containing medically important antimicrobials for use in non-food (companion), food-producing animals, or both, that are currently approved with over-the-counter marketing status. The guidance contains information - - to facilitate voluntary changes to the approved - - use of these drugs to prescription marketing status."

Later in GFI 263: "The voluntary process outlined in this guidance will help to ensure new animal drugs containing antimicrobials of human importance are administered only under veterinary oversight and only for therapeutic uses."

Documents from virtually any level of government, often including regulations or laws, nearly always contain language that is difficult to understand, and referral to other documents that are not included in the primary document one is trying to read. There is frequent reference in GFI 263 to Appendix A, the list of medically important antibiotics, with a caveat that "Appendix A reflects FDA's current thinking and thus is not static; FDA will periodically reassess and update this list." However, Appendix A is not found within GFI 263. I could find no evidence of recent updates anywhere.

I found Appendix A in GFI 152, with this statement on the 28th page of that document: "The rankings of drugs in Appendix A may be subject to change at any time when information becomes available that would impact those rankings. The sponsor may wish to consult with FDA regarding the ranking relevant to their proposed drug at the time the assessment is made." If this is identical to the language in the VFD, the sponsor refers to the manufacturer(s) of the antimicrobial drugs that need to be changed to Rx status.

It was my original intent to show Appendix A, the list of medically important antibiotics for treatment of humans, here. How could I forget so soon that Appendix A is quite lengthy? Therefore, you can see it at: https://www.fda.gov/media/69949/download
and then find it on pages 30 - 33 of that document, GFI 152.

However, a brief summary of the medically important antimicrobials in Appendix A follows on the next page:

The extensive list of medically important antimicrobials in Appendix A *includes* (again, the entire list occupies 4 pages): Penicillins, cloxacillins, amoxicillin, ampicillin, first through fourth generation cephalosporins, quinolones, fluoroquinolones including ciprofloxacin and norfloxacin, aminoglycosides, macrolides, clindamycin, tetracyclines, vancomycin, pyrazinamide, isoniazid, rifamycins, chloramphenicol, metronidazole, sulfa-trimethoprin, and polymixin B.

GFI 263 also states, "[following earlier regulations adopted] specific to the use of such drugs in food-producing animals, FDA believes it is appropriate to apply these same judicious use principles to the use of medically important antimicrobial drugs in all animals. - - The involvement of a veterinarian is needed because judicious use of antimicrobial drugs requires an accurate diagnosis of the bacterial disease that is present, or likely to be present, and the selection of a suitable antimicrobial drug to address that disease."

Timeline for voluntarily implementing changes

GFI 263 states, "FDA anticipates that sponsors of affected products should be able to have revised labeling approved that incorporates the changes discussed in this guidance within 2 years from the date of publication of the final version of this guidance. - - If we determine that adequate progress has not been made by the end of the 2-year timeframe, we will consider whether further action under the existing provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for addressing matters related to the safety of approved new animal drugs may be appropriate."

Note: Because the final version of GFI 263 has not been published, there is no stated anticipated date, and considering that this sometimes takes place long after preliminary publication, it is not yet clear when "2 years from the date of publication of the final version" might be. Also, such new FDA deadlines are often pushed back. Nevertheless, events in recent years suggest that this change to Rx antibiotics will eventually be adopted.

What does this mean for veterinarians, including dairy veterinarians?

One thing that surprised me when reading the details of this proposed change in comparison to the first news I heard about it was that it will include companion animals as well as food animals. I know many dairy and food animal veterinarians who work in group practices such that on some days they treat small animals for either several hours or all day, or they occasionally are asked to treat dogs, cats, or many other species on dairy farms.

In connection with another potential State of Utah issue before the Utah Veterinary Medical Association board and the state legislature, I recently asked a question that I also asked back in October 2015 of multiple FDA officials in the lead-up to adoption of the VFD rules. What is a companion animal; what are the species/definitions? A few sheep or goats, some 4H pigs that the kids did not want to sell after all, etc.? A herd of 5 llamas? A flock of 12 chickens that lay eggs but are treated like pets? In answer, the FDA and other authorities that regulate veterinary medicine have always responded that they did not know what defines a companion animal. Therefore the proposed regulation that all antimicrobials for all animals will be changed to Rx status probably simplifies life for dairy and food animal veterinarians, at least in one way. It will not be necessary to have OTC medications available or described as an option for some species, but Rx for others.

From my experience, this is another regulatory step such as AMDUCA (Animal Medicinal Drug Use Clarification Act) in 1994, subsequent clarifications of rules of extra-label drug use over the years, and more recently the VFD in 2017, that all highlight something critically important. A valid VCPR (Veterinarian-Client-Patient Relationship). This term has been discussed since I can remember, and was modified in 2012 to make it even more nebulous. But what exactly is really required to constitute a valid VCPR? Is it enforced?

Unless and until FDA and/or other agencies and authorities that regulate veterinary medicine and pharmaceuticals ever address what is really needed for a VCPR, the apparent aims of increased veterinary

insight and diagnoses before use of antimicrobials in animals, birds, fish, etc. are unlikely to be fully realized. The involvement of a veterinarian who observes the animals directly, diagnoses the disease(s) observed, including relevant clinical signs and likely differential diagnoses, and then prescribes antimicrobial drugs based on this timely familiarity with the animals does not always take place when animal owners obtain Rx drugs including antibiotics. This will continue, and quite possibly increase, unless a valid VCPR including reasonable familiarity with the disease on farms or in companion animals is both defined and enforced.

It is not easy to find data regarding what proportion of animal drugs are currently sold through veterinary practices versus other sources, including for prescription drugs. According to a 2015 Federal Trade Commission report, and subsequent reports by private market tracking organizations, the pet animal drug market has had a marked increase in the volume and proportion of sales of both OTC and Rx drugs through online sources, which I'm sure is not a surprise to anyone who has followed this to any degree.

The FTC report also extensively describes "diversion", which includes veterinarians willing to write a prescription, receive quantities of Rx drugs, then sell them to a secondary distributor. "For those veterinarians who engage in diversion, therefore, the profitability of diversion apparently outweighs any concerns about prosecution or sanctions." says the FTC. It is also clear that "industry stakeholders" disagree on whether veterinarians writing prescriptions to divert sales of Rx drugs to owners or farms they have never seen is "legal"; this part of the document makes no mention of a VCPR. The report concludes that "research produced scant evidence of significant enforcement efforts by the states", not even mentioning possible federal enforcement in cases of diversion of animal drugs, including Rx drugs.

Will the change benefit dairy and other veterinarians, or create more potential liability?

This is a major question, and I find that several of my colleagues have been wondering the same thing. The FDA wants more control by veterinarians over the use of medically important antimicrobials, including timely diagnostic procedures. This will only happen if Rx status of all such drugs in all animals does indeed require a valid VCPR, including veterinarians observing or being directly involved in diagnostic procedures on farms. Diversion of Rx medications will need to be eliminated or greatly reduced.

If this does take place, will this mean that veterinarians will indeed have more control and more influence on choices of antimicrobial treatments including for dairy cattle? Will each specific outbreak of disease, particularly increases in mastitis, respiratory disease, metritis or diarrhea have more direct diagnostic input before choosing antimicrobial treatment? Will veterinarians be able to charge somewhat more for the sale of Rx drugs? Competition with low cost one-day clinics, others performing veterinary procedures, and other sources of buying animal medications has reduced profitability for many veterinary practices. Will this change help offset that to keep veterinarians profitable and thus remaining in the profession for the benefit of society? There is no doubt that some consumer advocates and others would criticize this last point as financially unfair to society, and some veterinarians say that we do not need to make money from drug sales (these viewpoints are also addressed in the 2015 FTC report; we all hear these differing opinions as well.)

On the other hand, could it be that producers' recourse for meat or milk residue violations, perceptions of marked treatment failure, or other negative outcomes will focus more on possibly instituting legal action against veterinarians? During the early to mid-1990's, there were some initiatives regarding "Residue Avoidance" in the dairy industry that were largely successful. However, it was all too common then that regulatory personnel at various public forums and conferences for livestock producers stated directly that producers with antibiotic residue violations should "sue their veterinarian". Many lively discussions ensued, and the vast majority of producers did not sue their veterinarian; most dairy veterinarians and their clients have a great relationship. I hope and expect that if all animal drugs become Rx, resentment toward veterinarians will be minimal.

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Giving your feedback during the comment period

What is your opinion regarding all of this? I hope our readers will share their opinions, including with FDA, during the comment period ending 12/24/19. GFI 263 says:

Submit electronic comments to https://www.regulations.gov. (If you type GFI 263 into the search box, and then click on the long title that comes up, then choose Comment Now! on the upper right, you can type or copy comments, and upload files if you want.)

Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with docket number FDA-2019-D-3614.

I hope you all have a great holiday season and upcoming year in 2020.

Please let us know your comments and suggestions for future topics. I can be reached at (435) 760-3731 (Cell), or **David.Wilson@usu.edu**.

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