Antibiotics in Animals

By Suzanne O'Shea and Christin Garcia

Issue

Scientists generally agree that human use of antibiotics contributes to the development of antibiotic-resistant infections in people. There is disagreement about whether antibiotic use in food animals contributes to the problem. Given the potential risk, some advocate for strict limits: allowing antibiotic administration only after a particular animal has been diagnosed with disease. Others believe administering low levels of antibiotics in animal feed has not been shown to contribute to antibiotic-resistant infections in humans, but does play an important role in preventing disease in herds and ensuring the purity of the nation's food supply. Current regulations allow some antibiotic administration to entire herds through animal feed. Recent Food and Drug Administration actions suggest this freedom may be restricted in the future, but FDA has not indicated that extreme changes are likely.

Background

For decades, the use of antibiotics in food animals has been controversial. In 1973, FDA promulgated a regulation stating it would propose to revoke approval of antibiotics intended to increase the rate of animal weight gain, or to prevent animal disease, unless data were submitted to "resolve conclusively" the issues concerning the drugs' safety to man and animals.[1] In 1977, under this regulation, FDA proposed to withdraw approval of all uses of penicillin in animal feed and most uses of tetracycline. Before FDA could take action Congress

Suzanne O'Shea focuses her practice in life science initiatives, and advises on pre- and postmarket regulatory requirements for FDA regulated products.

Christin Garcia defends product liability and related claims, often focused on the effects medicines or chemicals have on health and risk.

intervened, directing the agency to refrain from withdrawing approval until further research could be done. Several antibiotics remain approved for use in animal feed for indications such as "growth promotion and feed efficiency."[2] Many such antibiotic products are over-the-counter (OTC), meaning no veterinarian involvement is required for their use.

FDA's Center for Veterinary Medicine (CVM) has issued several documents suggesting how it now intends to navigate this controversial territory. In 2011 a lawsuit entered the picture, seeking to force FDA's hand.

Why the issue is important?

The growth of serious antibiotic–resistant infections in humans is a significant global public health concern. Scientists disagree about how antibiotic use in food animals contributes to the growth of these infections. Extreme use restrictions, while justified in some peoples' eyes, also could result in significant detrimental health consequences for animals and the purity of the nation's food supply.

How might the issue be resolved in 2012?

With a pending lawsuit and increased public focus on the potential risk, there is indication that FDA will move towards greater control of the use of antibiotics in animals, particularly for growth promotion and feed efficiency. FDA has not expressed an intent, however, to stop antibiotic use for disease prevention.

In 2003, CVM issued Draft Guidance #152, Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to their Microbiological Effects on Bacteria of Human Health Concern,[3] which provides a framework for qualitatively evaluating the risk to humans of using antibiotics in animals when there is a lack of substantial data. Under this approach, various factors such as the probability that resistant bacteria are present in the target animal as a consequence of drug use, the probability for humans to ingest the bacteria in question, and the probability that human exposure to resistant bacteria will result in adverse human health consequences are ranked as low, medium or high. This guidance also provides a ranking of the importance of particular antimicrobial drugs, indicating FDA's greater concern about antibiotics that are critically important to human health. Guidance #152 is primarily directed toward sponsors seeking approval of antibiotics for use in animals, but provides no information on acceptable indications for use.

In 2010, CVM issued Draft Guidance #209, The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals.[4] This guidance applauds efforts by industry and veterinary groups to institute guidelines for the use of antibiotics in animals, but states that FDA believes an additional principle is required: "(t)he use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that are considered necessary for assuring animal health. In light of the risk that antimicrobial resistance poses to public health, FDA believes the use of medically important antimicrobial drugs in food-producing animals for production purposes (e.g. to promote growth or improve feed efficiency) represents an injudicious use of these important drugs." Of particular note is the Guidance's further statement that "(a)lthough some may have concerns that the use of medically important antimicrobial drugs in food-producing animals for disease prevention purposes is not an appropriate or judicious use, FDA believes that some prevention indications are necessary and judicious."[5] The guidance states that prevention claims should be supported by evidence of: effectiveness, consistency with accepted veterinary practice, a specific etiologic agent, appropriate targeting, and no reasonable alternatives.

Draft Guidance #209 includes a second proposed principle: "(t)he use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that include veterinary oversight or consultation…. Veterinarians can play a critical role in the diagnosis of disease and in the decision-making process related to instituting measures to treat, control, or prevent disease."[6]

In this connection, it should be noted that in March 2010, CVM issued an advanced notice of proposed rulemaking requesting comments on possible changes to the process used with Veterinary Feed Directive (VFD) drugs.[7] VFD drugs are intended for use in or on animal feed and are limited to use under the supervision of a veterinarian, but are not prescription drugs and are not subject to State pharmacy laws.[8] According to the ANPR, FDA has received numerous comments that the VFD process is overly burdensome, and that it may become particularly problematic in the future as more VFD drugs are approved. It would seem logical that FDA wishes to streamline this process if it will direct more drugs through its path.

Draft Guidance #209 contains a strong suggestion that CVM intends to evaluate antibiotics currently approved for growth promotion or improvement of feed efficiency using the framework described in Guidance #152, and pursue formal or informal action when warranted.[9] A formal action to withdraw an NADA is a difficult and time consuming process, as FDA has the initial burden of producing evidence sufficient to raise

serious questions about the safety of the particular drug and the manufacturer has opportunities to present additional data.[10] Yet FDA also may face legal challenges for deciding not to take action. A lawsuit brought in May 2011 by the Natural Resources Defense Council and others, in connection with penicillin and tetracycline use, is pending before a federal court in New York.[11]

Conclusion

In 2012 we expect to see increased evaluation of approved antibiotic drugs labeled for improved feed efficiency or growth production. With appropriate data supporting the use of antibiotics in preventing disease, the possibility of converting approved OTC drugs into VFD drugs is an option that may be considered more frequently. CVM has already taken a similar step in 2012, with the issuance in January of the order prohibiting extralabel uses of cephalsporin drugs in certain food-producing animals.[12] The circumstances were not identical, but the concern was the same: "… it is likely that the extralabel use of cephalosporins in certain food-producing animal species is contributing to the emergence of cephalosporin- resistant zoonotic foodborne bacteria."

1. 21 CFR § 558.15.
2. See 21 CFR Part 558, Subpart B.
3. Available at: http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052519.pdf.
4. Available at: http://www.fda.gov/downloads/animalveterinary/guidancecomplianceenforcement/guidanceforindustry/ucm216936.pdf.
5. Guidance #209, page 16
6. Guidance #209, page 17
7. See Federal Register of March 29, 2010, 75 FR 15387.
8. See description of VFD drugs in the Federal Register of December 8, 2000, 65 FR 76924.
9. Guidance #209 at 14
10. For a summary of the NADA withdrawal process, along with a description of the five year process to withdraw approval of the use of Enrofloxin in poultry, see the September 2011 Antiobiotic Resistance report from the Government Accountability Office, GAO-11-801, at pp. 24-25.
11. US District Court, SDNY, Case # 1:11-cv-03562-THR. As of January 2012, cross-motions for summary judgment were pending. FDA withdrew the relevant Notice of Opportunity for a Hearing in the Federal Register of December 22, 2011 (76 FR 79697).
12. See Federal Register of January 6, 2012, 77 FR 735.