

Review of regulations and indications for the use of in-feed antimicrobials for production animals

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doi.org/10.2460/javma.22.07.0300

Antimicrobials have been fed to livestock for more than 60 years. Veterinarians and producers saw tremendous gains in health and performance, and usage became widespread. Over time, improved management reduced some of the benefit of many feed-through antimicrobials except for a few important diseases. As a result of concerns about antimicrobial resistance, the US FDA restricted the use of medically important antimicrobials. Starting in 2017, medically important antimicrobials were restricted to therapeutic purposes only, and only under the order of a veterinarian. The aim of this review is to provide an overview of commonly used antimicrobials in livestock feed and regulatory changes regarding the veterinary feed directive. When used judiciously, in-feed antimicrobials are an important tool to ensure the health and welfare of food animals while preserving the effectiveness for animals and humans.

Since the discovery that chlortetracycline improved the growth rate of animals, feed antimicrobials have been used in animal feed.¹ Initial approvals by the US FDA allowed for inclusion of in-feed antimicrobials without veterinary oversight.² At that time, regulatory concerns were focused on hypersensitivity reactions in humans resulting from antimicrobial residues in meat, rather than on the development of widespread resistance.³ During the 1970s, antimicrobials became widely used for animal production primarily because they reduced the cost of production.⁴ Antimicrobial resistance is a public health crisis that is associated with the widespread use of antimicrobials in humans and animals.⁵ A reduction in antimicrobial use in food animal production results in a modest decrease in antimicrobial resistance.⁶ The regular use of antimicrobials for production purposes has been criticized for decades, and in 2012, the FDA initiated that new approvals of antimicrobials for food animals required a risk assessment for the development of resistance for medically important antimicrobials.⁷ In 2012, the FDA began the process to restrict the usage of antimicrobials in food animals by (1) removing label claims associated with growth promotion and (2) requiring veterinary oversight via the veterinary feed directive (VFD) for all medically important antimicrobials by January 1, 2017.⁸

Regulations

In 2012, the FDA issued Guidance for Industry (GFI) 209, establishing the FDA's position that medically important antimicrobials should not be used

for production enhancement (rate of gain or feed efficiency), and that veterinary oversight should be required when using medically important antimicrobials for treatment, prevention, or control.⁸ This policy went into effect January 1, 2017. This guide defined therapeutic purposes as treatment, control, or prevention of disease.⁸ Besides removal of growth promotion claims, the other outcome of GFI 209 was to move medically important feed antimicrobials from being available over the counter to under the direction of the veterinarian via the VFD.⁸

In October 2015, the FDA amended the federal regulations that had been established in 1996 and issued new rules for the VFD process to accommodate the more routine use of feed-grade antimicrobials.⁹ Starting January 1, 2017, livestock producers require a VFD in place to buy or use medically important antimicrobials in animal feed.

A VFD order is issued by a licensed veterinarian that has knowledge of the health and management of the animals. According to federal regulations, there must be a valid veterinary-client-patient relationship prior to issuing a VFD. The requirements of a veterinary-client-patient relationship are as follows¹⁰:

1. A veterinarian has assumed the responsibility for making medical judgments regarding the health of an animal or animals 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 animals by the veterinarian to initiate at least

a general or preliminary diagnosis of the medical condition of the animals.

3. The practicing veterinarian is readily available for follow-up 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 animals by virtue of examination of the animals or by medically appropriate and timely visits to the premises where the animals are kept.

A valid VFD must contain the following information in the documented directive.⁹ The directive can either be written on a paper copy or transmitted as an electronic document. However, telephone orders are not allowed.

- Veterinarian's name, address, and phone number
- Client's name, address, and phone number
- Name of VFD drug
- Level of VFD drug in the feed
- Duration of use
- Species and production class of animals to be fed
- Label indication that the VFD is issued for
- Cautionary statement, if any
- Approximate number of animals
- Premises at which the animals specified in the VFD are located
- An affirmation of intent for combination VFD drugs
- Withdrawal time
- Date of VFD issuance
- Expiration date
- Veterinarian's signature
- The statement: "Use of feed containing this veterinary feed directive (VFD) in a manner other than directed on the labeling (extra-label use) is not permitted."

As stated extra-label use of feed medications is not permitted by federal law and, unlike prescription drugs, a veterinarian cannot write an order for extra-label use. Extra-label use includes altering the dose, indication, species, or duration of use.

Minor Species

As with the application of most rules, there is an exception to no extra-label drug use with feed medications. The FDA classifies horses, dogs, cats, cattle, pigs, chickens, and turkeys as major species. Any other animal species is considered a minor species for which the FDA sometimes makes exceptions in drug approval and enforcement. Compliance Policy Guide (CPG) 615.115 Extralabel Use of Medicate Feeds for Minor Species provides guidance for veterinarians and enforcement personnel on this issue.¹¹ The justification is that some minor species where feed medications may be the only practical method to medicate animals (game animals) or there are very few approved drugs available (fish, game birds, etc). Therefore, a veterinarian may determine that

extra-label use is needed to prevent suffering or death. It is important to remember that this CPG does not make extra-label usage legal; it merely allows for enforcement discretion by the regulatory agent.

Although CPG 615.115 provides a framework to allow for extra-label use in minor species, there are no clear recommendations of what is or is not allowed. Therefore, it is up to local inspectors to interpret what the CPG mean. Prior to writing a VFD for a minor species, veterinarians should have a discussion with their local inspector regarding how they would interpret and enforce this CPG.

Indications

Most feed antimicrobials have a label indication for either control or treatment of a bacterial disease. There are a few nonmedically important antimicrobials (such as ionophores or carbadox) that, in addition to a disease label, also still maintain a production label for improved feed efficiency. Because nonmedically important antimicrobials do not fall under the restrictions of FDA GFI 209, they are still able to maintain a production claim.⁸ Ionophore antimicrobials are typically labeled to prevent or control coccidiosis in poultry or ruminants and an increased performance in cattle only. For both the prevention and control of coccidiosis, and the production claims, the label directions indicate that the medication should be fed continually. It is important to remember that ionophore antimicrobials are toxic to monogastric mammals, and mixing errors can lead to toxicity in poultry and ruminants. Other nonmedically important antimicrobials include bambermycin, bacitracin, carbadox, and flavomycin, although they are not used as regularly as ionophore antimicrobials.

Indications for Use

Cattle

Tylosin and chlortetracycline are the most common medically important feed antimicrobials for cattle. Tylosin has a label indication for the reduction of liver abscesses in beef cattle. Research in the late 1960s demonstrated that tylosin was effective at reducing liver abscesses, and this activity likely explained the improved performance seen when it was included in cattle diets.¹² In 2011, approximately 70% of US feedlot cattle received tylosin in their feed.¹³ It has been reported that tylosin can reduce the incidence of liver abscesses by 30%.¹⁴ The label for tylosin in cattle recommends continual feeding of the antimicrobial for reduction of liver abscesses. In 2018, the FDA released a 5-year plan to support antimicrobial stewardship in veterinary settings, and one of the objectives of this plan was define the duration of use for products without a defined duration of use.¹⁵ The administration of tylosin to reduce liver abscesses highlights the difficulty in the judicious use of antimicrobials that reduce a harmful animal disease while remaining cognizant of the need to manage antimicrobial resistance issues for medically important antimicrobials.

Similarly, in most circumstances, chlortetracycline label approvals do not include a duration of use. The approval for reduction in liver abscesses is similar to tylosin, and approvals for control of bacterial pneumonia and anaplasmosis do not state a defined duration of use. The only indication for cattle with a defined duration of use is for treatment of bacterial enteritis and pneumonia, which is for 5 days. After implementation of FDA GFI 209, the sale of tetracycline-class antimicrobials dropped from 5.8 million kg to 3.5 million kg,¹⁶ implying that the removal of the growth promotion claims for this class of antimicrobials caused a significant reduction in sales. Chlortetracycline continues to be used for controlling anaplasmosis and treating respiratory disease.

Other medically important antimicrobials are available for feed use in cattle, such as oxytetracycline, sulfa drugs, and penicillin, but with limited use. Neomycin or oxytetracycline, or both, are sometimes incorporated into medicated milk replacers for calves to treat or control enteritis.

Poultry

Feed-based antimicrobials are severely limited in poultry because of their short production span and strict regulations on withdrawal periods. In meat-type poultry (broilers and turkeys), the list of antimicrobials that require a VFD include chlortetracycline, halofuginone, lincomycin, neomycin or oxytetracycline, oxytetracycline, penicillin, sulfa-type drugs, and virginiamycin. The rest of them are primarily antiparasitics, predominantly with the use of coccidiostats, and are not considered antimicrobials. Many are not considered medically important antimicrobials. The most common use of feed-based antimicrobials is for treatment against gram-negative bacteria, such as *Escherichia coli* infections, and against enteritis and systemic infections resulting from gram-positive bacteria, such as *Clostridia* spp. In general, tetracyclines and sulfa drugs are used in young chickens and turkeys. In mature, laying egg-type chickens, the only feed-grade antimicrobial that requires a veterinary prescription is chlortetracycline limited to the Aureomycin brand. The only other exception of antimicrobials fed in poultry are type A medicated feeds that do not require prescriptions. An example of this is bacitracin methylene disalicylate, which can be fed continually until up to 40 weeks of age. Bacitracin methylene disalicylate has been indicated for use in controlling clostridial enteritis (eg, necrotic enteritis, quail enteritis, focal duodenal necrosis) in both meat and egg-type poultry. Feed-grade medication that are FDA approved for laying hens have a 0-day egg withdrawal when used per label instructions, and thus extra-label use is not tolerated if there are no guidelines for egg withdrawal. Extra-label drug use is predominantly done through administration of antimicrobials via the drinking water. For specific use in poultry, please consult with VetGram on the Food Animal Residue Avoidance and Depletion website or FDA Animal Drugs website in conjunction with consulting label instructions prior to use.¹⁷ The use of medically important

in-feed antimicrobials has decreased significantly in the poultry industry with the increase in demand for antibiotic-free/raised-without-antibiotics poultry products and improved antibiotic stewardship. In a retrospective analysis performed between 2013 and 2017, tetracycline use in the feed of broiler chickens dropped by 95% from 2013 to 2017, and decreased by 67% over the same period in turkeys, and continues to trend toward decreased usage with the use of alternatives to antibiotics.^{18,19}

Swine

The tetracycline class of antimicrobials (chlortetracycline, oxytetracycline, tetracycline) represents the significant majority of the medically important antimicrobials used in swine today. A voluntary survey of antimicrobial use data estimated that the tetracycline class represented approximately 60% of all antimicrobials used in 9 large production systems that represented 20% of the US swine industry in 2016 and 2017.²⁰ The majority of tetracycline use is comprised of chlortetracycline and oxytetracycline. Tetracycline class antimicrobials are used most commonly to treat *Pasturella multocida* as a secondary bacterial pathogen in nursery and finishing respiratory disease. Other medically important feed-grade antimicrobials used commonly include macrolides, such as tylosin, and tylvalosin and lincosamides, which are used to fight porcine respiratory disease as well as enteric pathogens such as swine dysentery or porcine ileitis, caused by *Lawsonia intracellularis* infection. Implementation of GFI 209 saw the sale of all medically important in-feed antimicrobials for swine decrease by 22% from 2016 to 2020 as a result of the loss of production claims (growth promotion) for medically important antimicrobials.¹⁶ The regulations also allowed producers and veterinarians to review feed medication protocols and look for opportunities to use medically important antimicrobials more judiciously.

Conclusion

In-feed antimicrobials are a valuable tool to prevent, control, or treat disease in animals. Some benefit in performance reported in early literature and approvals may have been the result of decreasing subclinical disease processes. Improvements in production practices, facilities, and management have improved the overall health of animals such that growth promotion indications are not the primary purpose of use. GFI 209 and the VFD process has reduced significantly the amount of feed medications used without adversely affecting overall health.

Acknowledgment

No external funding was used in this study.
The authors declare that there are no conflicts of interest.

References

1. Jukes TH. *Antibiotics in Nutrition*. Medical Encyclopedia, Inc; 1955:128.

2. Jones F, Ricke S. Observations on the history of the development of antimicrobials and their use in poultry feeds. *Poult Sci*. 2003;82(4):613–617. doi:10.1093/ps/82.4.613
3. Ainsworth GC, Austwick PKC. Response to the proposed amendments to the penicillin act. *Vet Rec*. 1953;65:166.
4. Council for Agricultural Science and Technology. *Antibiotics in Animal Feeds*. Report No. 88. Council for Agricultural Science and Technology; 1981.
5. CDC. *Antibiotic Resistance Threats in the United States*. US Department of Health and Human Services, CDC; 2019.
6. Tang KL, Caffrey NP, Nobrega DB, et al. Restricting the use of antibiotics in food-producing animals and its associations with antibiotic resistance in food-producing animals and human beings: a systematic review and meta-analysis. *Lancet Planet Health*. 2017;1:e316–e327. doi:10.1016/S2542-5196(17)30141-9
7. #152 Guidance for industry: evaluating the safety of antimicrobial new animal drugs with regard to their microbiological effects on bacteria of human health concern. US FDA. Department of Health and Human Services Center for Veterinary Medicine. Last modified October 23, 2003. Accessed June 12, 2022. <https://www.fda.gov/media/69949/download>
8. #209 Guidance for industry: the judicious use of medically important antimicrobial drugs in food-producing animals. US FDA. Department of Health and Human Services Center for Veterinary Medicine. Last modified April 13, 2012. Accessed June 12, 2022. <https://www.fda.gov/media/79140/download>
9. Veterinary feed directive. Code of Federal Regulations. Last modified June 3, 2015. Accessed June 12, 2022. <https://www.federalregister.gov/articles/2015/06/03/2015-13393/veterinary-feed-directive>
10. Valid veterinarian–client–patient relationship. Code of Federal Regulations. Last modified January 3, 2017. Accessed June 12, 2022. [https://www.ecfr.gov/current/title-21/chapter-I/subchapter-E/part-530/subpart-A/section-530.3#p-530.3\(i\)](https://www.ecfr.gov/current/title-21/chapter-I/subchapter-E/part-530/subpart-A/section-530.3#p-530.3(i))
11. Compliance Policy Guide: Sec. 615.115 Extralabel use of medicate feeds for minor species. US FDA. Department of Health and Human Services Center for Veterinary Medicine. Last modified December 2016. Accessed June 12, 2022. <https://www.fda.gov/media/71960/download>
12. Simpson KE. *Feeding tylosin in attempting to control liver abscesses*. Master's thesis. Texas Tech University; 1969.
13. Feedlot 2011 Part IV: health and health management on US feedlots with a capacity of 1,000 or more head. USDA-APHIS-VS-CEAH-NAHMS. Last modified September 2013. Accessed June 12, 2022. https://www.aphis.usda.gov/animal_health/nahms/feedlot/downloads/feedlot2011/Feed11_dr_PartIV_1.pdf
14. Wileman BW, Thomson DU, Reinhardt CD, Renter DG. Analysis of modern technologies commonly used in beef cattle production: conventional beef production versus nonconventional production using meta-analysis. *J Anim Sci*. 2009;87(10):3418–3426. doi:10.2527/jas.2009-1778
15. Supporting antimicrobial stewardship in veterinary settings: goals for fiscal years 2019–2023. US FDA. Department of Health and Human Services Center for Veterinary Medicine. Last modified September 2018. Accessed June 12, 2022. <https://www.fda.gov/media/115776/download>
16. 2020 Summary report on antimicrobials sold or distributed for use in food-producing animals. US FDA. Department of Health and Human Services Center for Veterinary Medicine. Last modified December 2021. Accessed June 12, 2022. <https://www.fda.gov/media/154820/download>
17. Food animal residue avoidance and depletion species page. Accessed August 22, 2022. <http://www.usfarad.org/treating-layers.html>
18. Singer RS, Porter LJ, Schrag NFD, Davies PR, Apley MD, Bjork K. Estimates of on-farm antimicrobial usage in broiler chicken production in the United States, 2013–2017. *Zoonoses Public Health*. 2020;67(suppl. 1):22–35. doi:10.1111/zph.12764
19. Singer RS, Porter LJ, Schrag NFD, Davies PR, Apley MD, Bjork K. Estimates of on-farm antimicrobial usage in turkey production in the United States, 2013–2017. *Zoonoses Public Health*. 2020;67(suppl. 1):36–50. doi:10.1111/zph.12763
20. Davies PR, Singer RS. Antimicrobial use in wean to market pigs in the United States assessed via voluntary sharing of proprietary data. *Zoonoses Public Health*. 2020;67(suppl. 1):6–21. doi:10.1111/zph.12760