The Veterinary Feed Directive Rules for Veterinarians

A Practical Guide for the Practicing Veterinarian

Lance Roasa, DVM, MS, JD

ABSTRACT

The transition of commonly used antibiotics away from production based - label claims to Veterinary Feed Directive (VFD) status is one of the largest regulatory changes to food animal veterinary practice in decades. This purpose of this document to aggregate information, aid veterinarians and their practices in making the transition, and provide practical solutions to questions created by the new VFD rules

Oct. 31, 2016

Why are these changes occurring?

The VFD rules are designed to give veterinary oversight into medically important antibiotics.

The Food and Drug Administration (FDA) is responsible for overseeing the marketing and use of drugs. Historically, two classifications of drugs, over the counter (OTC) and prescription, were available to drug manufacturers applying to market and sell drugs in the United States. Once the FDA approves a drug through the appropriate classification, the drug's label places requirements and restrictions for its use and that label controls the marketing and use of that drug. The designator "medically-important antibiotics" does not apply to all antibiotics, just those that are deemed useful to human medicine and are at-risk to antibiotic resistance.[1]

In 1996 Congress created a third classification by which drug manufacturers could bring drugs to market, the VFD.[2] Few drug manufacturers utilized the VFD pathway over the next 20 years.[3] However, with a series of guidance documents, the FDA announced its intention to request that manufacturers voluntarily transition OTC labeled drugs to the VFD label claim. This cumulated in April 2015 with a final rule promulgated by the FDA that updated the requirements for using VFD drugs

[1] For a list of "medically-important" antibiotics from the FDA website, see Attachment 1. Last accessed on Oct 31, 2016 at http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/ucm482107.htm.

[2] See generally the Animal Drug Availability Act of 1996, which amended the Food Drug and Cosmetic Act of 1938 at 21 USC 9 §§ 301, 321, 354 and 360b.

[3] It is important to note that a VFD is not analogous to a prescription and using the term "prescription" or "prescribe" raises additional requirements for the veterinarian found in many state veterinary practice acts and regulations. For example, Texas's Administrative Code allows disciplinary action for a veterinarian who "orders a prescription drug or controlled substance for the treatment of an animal without first establishing a veterinarian-client-patient relationship 4 Tex. Admin. Code § 801.402(13)

and the respective responsibilities of veterinarians, producers and feed distributors.[4]

Recently, the FDA has published several Guidance For Industry documents designed to aid the transition process.[5] These guidance documents are written in plain language and help apply the new rules to actual scenarios. The guidance documents, however leave some information gaps in the real world practice of food-animal medicine. This document will summarize the FDA's publications and supplement practical information where needed.

The FDA and World Health Organization have determined that medical evidence links antibiotic resistance in humans to antibiotic use in food producing animals.

Understanding the reasoning behind the rules may help a veterinarian's appreciation of the changes and assist with compliance. The reasoning behind the current transitioning of drug labeling to VFD status is the concern and evidence regarding antibiotic resistance in humans. As early as 1970, the FDA began to examine the safety and efficacy of penicillin and tetracycline used in animal feeds.[6] In 1977 the FDA proposed public hearings on the matter.[7] Shortly thereafter, Congress directed studies regarding the possibility of human antibiotic resistance to

[4] See 21 CFR § 558.6
[5] See Attachment 2. Guidance for Industry Document # 209, last accessed Oct. 31, 2016 at http://www.fda.gov/downloads/animalveterinary/guidancecomplianceenforcement/guidanceforindustry/ucm216936.pdf. See also Attachment 3, Guidance for Industry Document #213, last accessed at Oct. 31, 2016 at http://www.fda.gov/downloads/animalveterinary/guidancecomplianceenforcement/guidanceforindustry/ucm299624.pdf.
[6] *NRDC, Inc. v. FDA*, 760 F.3d 151 (2d Cir. 2014).
[7] *Id*. at 154.

begin.[8] The FDA delayed the hearings, pending the results of the research. Ultimately, the FDA never held the hearings regarding antibiotic use in feeds and nearly 40 years later, advocacy groups filed lawsuits demanding that the FDA hold the required hearings.[9]

In the 45 years since researchers have begun to examine the issue of human antibiotic resistance stemming from sub-therapeutic use in food animal feeds, the FDA has used task forces, expert panels, WHO reports, Government Accountability Office reports, the National Research Council reports, Institute of Medicine reports, and peer reviewed scientific literature to provide a evidentiary framework for the rule.[10] Veterinarians interested in the research and reasoning behind the conclusion are encouraged to read Guidance for Industry Document #209, where the FDA outlines its thinking and cites peer-reviewed literature that the rule is based upon.[11] The scientific debate concerning the link between antibiotics in animal feeds and antibiotic resistance bacteria is human medicine is ongoing.[12] The issue is complex and multifaceted. Normal dirt flora, metals such as Zinc, and non-antibiotics such as salicylate all potentially contribute to human antibiotic resistance.[13] Additionally, human use of antibiotics, veterinary use in non-food species, and cross-resistance

[8] *Id.*
[9] *Id*. at 156
[10] See Guidance for Industry document #209 at 19.
[11] Guidance for Industry Document #209.
[12] Nancy E. Halpern, *Antibiotics in Food Animals: The Convergence of Animal and Public Health, Science,* Policy, Politics and the Law, 14 Drake J. Agric. L. 401 (2009); M.A. McCrackin, Kristi L. Helke, Ashley M. Galloway, Ann Z. Poole, Cassandra D. Salgado & Bernadette P. Marriott. *Effect of Antimicrobial Use in Agricultural Animals on Drug-resistant Foodborne Campylobacteriosis in Humans: A Systematic Literature Review*, Critical Reviews in Food Science and Nutrition, 56:13, 2115-2132 (2016).
[13] Meghan Davis, Lainie Rutkow, *Regulatory Strategies To Combat Antimicrobial Resistance of Animal Origin: Recommendations for a Science-Based U.S. Approach*, 25 Tul. Envtl. L.J. 327 at 339. (2012).

even across antibiotic classes create continued resistance despite complete antibiotic bans.[14]

Although the research is ongoing, and the scientific debate ensues, the FDA has promulgated rules that will carry the force of law beginning Jan. 1, 2017. A number of commenters have written that the VFD rules don't go far enough and that they leave large loopholes where antibiotics will continue to be fed for preventative but non-production reasons.[15] Regardless of the debate and the unsettled science behind the rules, veterinarians have the responsibility to know the rules, and abide by their requirements. Veterinarians will be in a position of oversight and education for the entire VFD process. This oversight component has thrust veterinarians into a position where they stand between feed distributors and producers who use antibiotics in their animals. This position will cause inconveniences and even disputes between the parties. However, this is designed to provide oversight and involvement by the veterinarian. This involvement could lead to new means to show how a veterinarian's input could benefit the producer, not hinder them. Veterinarians who grasp this opportunity should see growth in other practice areas where they will regularly have the opportunity to display their knowledge. However, this increased responsibility has the potential to bring additional liability

[14] *Id*. at 375. Discussion the ban of fluorquinolones in poultry and persistence of antibiotic resistance
[15] Lisa Heinzerling. *The FDA's Continuing Incapacity on Livestock Antibiotics*, 33 Stan. Envtl. L.J. 325 (2014); Amanda Belanger, *A Holistic Solution for Antibiotic Resistance: Phasing out Factory Farms in Order to Protect Human Health*, 11 J. Health & Biomed. L. 145 (2015); Kayla Despenes, *A supersized solution to superbugs: Preventing a post-antibiotic era by optimizing consumer demand*. 76 U. Pitt. L. Rev. 569 (2015); Nathalie Prescott, *Antibiotics: It's What's for Dinner*, 28 Geo. Envtl. L. Rev. 307 (2016); Lauren Orrico, *Squashing the superbugs: A proposed multifaceted approach to combatting antibiotic –resistant bacteria*, 27 J.L. & Health 259 (2014); Sarah Hagg. *FDA industry guidance targeting antibiotics used in livestock will not result in judicious use or reduction in antibiotic resistant bacteria*, 26 Fordham Envtl. Law Rev. 313 (2015); Nikki Sanford, *The battle against antimicrobial drug resistance: analyzing recent developments and the necessity for major agricultural reforms,* 40 Wm. & Mary Envtl. L. & Pol'y Rev. 989 (2016).

to veterinarians and their practices, mitigating that risk will be discussed fully below.

What are the practical aspects of the VFD process that a veterinarian needs to know?

The process and specific requirements of the VFD process are well characterized in the reference materials provided.[16] Please refer to this practice summary sheet for the details regarding writing, issuing and storing the VFD.[17] Below are issues that are not addressed by either the FDA or other reference materials regarding the VFDs, but should nonetheless be incorporated into the veterinarian's plan for VFD compliance.

A Veterinary Client Patient Relationship is needed before issuing a VFD

The VFD Rules require that a Veterinary Client Patient Relationship (VCPR) be established before issuing a VFD.[18] Many states have specific requirements for establishing a VCPR in their practice acts or applicable regulations.[19] For other states that don't address the VFD process directly, a federal regulation provides a VCPR requirement for VFD drugs.[20] Regardless, the underlying theme is that the

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[16] See Attachment 4 for summary sheets developed by stakeholders. Last accessed Oct 31, 2016. https://www.avma.org/KB/Resources/Pages/VFD123.aspx; http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/ucm449019.htm http://www.farad.org/regulatory/vfd.asp; http://www.usfarad.org/vfd.html.

[17] See Attachment 5 for a veterinary practice specific summary sheet.

[18] 21 CFR § 558.6(b)(1).

[19] See Attachment 6, which is continually updated at http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/ucm460406.htm. Last accessed Oct 31, 2016.

[20] The VCPR required federally states, "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)." 21 § 530.3(i)(2)) The Federal rule goes on, "[s]uch a relationship can exist only when the veterinarian has recently seen and is personally acquainted with the keeping and care of the

"issuing veterinarian is assuming the responsibility for making medical judgments regarding the health of the animal(s)" and "the client has agreed to follow the instructions of the veterinarian."[21]

The federal VCPR requirement continues with specifics as to how the veterinarian is to assume the responsibility. The key language in the federal VCPR that a veterinarian must be aware of is "there is sufficient knowledge of the animal"… "by virtue of examination and/or medically appropriate and timely visits to the premises where the animal(s) are kept." In the daily practice of food animal and mixed animal practice it is practically impossible to perform physical examinations on every animal that will be fed medicated feed. Concurrently, in many veterinary practices, an ongoing client relationship is established with many clients through visits to their facilities. The VCPR regulatory language leaves clinical discretion to the veterinarian to determine the amount of "sufficient knowledge" of the facility to issue a VFD.[22]

Another potentially impactful requirement of the VCPR is the necessity for a valid license in the state where the animals are fed.[23] This mean that veterinarians overseeing animals on feed in numerous states, even if those animals are owned by

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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." 21 CFR § 530.3(i)(3).

[21] *Id.*

[22] Ultimately, the veterinarian's license to practice veterinary medicine is regulated under the state's practice act and subject to actions for issuing VFDs not incompliance with the state's VCPR requirements. See pg. 3 Interview with Michael Taylor FDA Deputy Commissioner for Foods and Veterinary Medicine and William Flynn Deputy Director for Science Policy in the FDA's Center for Veterinary Medicine at http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/ucm448871.htm. Last Accessed Sep 15, 2016,

[23] 21 CFR § 558.6 (b)(1) states the veterinarian must "be licensed to practice veterinary medicine."

the same entity, must maintain licensure in all states where the medicated feed or water is fed or consumed.

Lastly, the federal VCPR requirement states that the issuing veterinarian be "readily available for follow up in case of adverse reactions or failure of the regimen of therapy."

The veterinarian should regularly visit the facility to maintain a valid VCPR.

Neither the rule creating the VFD, the federal VCPR requirement, nor the FDA's publications state a hard and fast rule for the frequency of visits that a veterinarian needs to retain the "sufficient knowledge" to issue VFDs. However, the maximum time before expiration of the VFD is 6 months from the date of issuance.[24] A proposed guideline for maintenance of a VCPR could state that maximal time between facility visits is 6 months, or the applicable expiration date.

When on the facility, the veterinarian can use this opportunity for education, maximizing return and showing value for veterinary advice and input to the producer. While on the facility, the veterinarian could check animal husbandry items such as housing conditions, animal handling, nutrition, vaccination protocols and other routine items. Properly addressed, these areas can provide increased returns through improved animal welfare. A knowledgeable veterinarian in these areas could provide great value for the producer and could potentially offset the cost of the VFD. Next, for concentrated animal feeding operations, amount of pen space, manure disposal practices, water access and runoff could all contribute to

[24] See 21 CFR § 558.6(b)(3)(v) and Guidance for Industry Document #120 at 10.

antibiotic residues in the environment. Some published research papers discuss the possibility that antibiotics and their metabolites, excreted via urinary and fecal routes, as a potential pathway for building antibiotic resistance.[25] The veterinarian could educate and instruct the producer regarding these practices, which could have significant impact on future actions and potential producer liability.

At the very least, making and documenting recommendations for facilities with deficient welfare practices and environmental issues is an important part of the onsite veterinary practice, however it is unaddressed in a cursory glance of the VFD rules. An understanding of the current legal environment facing CAFOs may help veterinarians reduce liability for their production animal clients.

The client is the person responsible for feeding and caring for the animals

Although the VCPR requires communication between the veterinarian and the client, determining the client in many food animal situations may be confusing. Animals may be owned by the facility, a distant producer with retained ownership, or a corporate entity. In these cases, it is impractical for a veterinarian to contact and form a relationship with those owners. For simplicity, the FDA has determined that the client may be the actual owner or the caretaker.[26] Consequently, the person or entities paying the veterinary bills or the legal owner of the animals may not be the "client" for purposes of the VFD.

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[25] Megan F. Davis, Lainie Rutkow, *Regulatory Strategies To Combat Antimicrobial Resistance of Animal Origin: Recommendations for a Science-Based U.S. Approach*, 25 Tul. Envtl. L.J. 327 at 339, 379. Meghan F. Davis et al., *An Ecological Perspective on U.S. Industrial Poultry Production: The Role of Anthropogenic Ecosystems on the Emergence of Drug-Resistant Bacteria from Agricultural Environments*, 14 Current Opinion Microbiology 244, 244-45 (2011).
[26] 21 CFR § 558.3(b)(7).

The use of production label claims will be phased out and only treatment, control or prevention claims will be allowed.

A significant impact on the use of many antibiotics is the transition from production based label claims, such as "feed efficiency or "increased weight gain" to therapeutic label claims. Potential therapeutic label claims include "prevention" "treatment" and "control" of a particular disease. For example, the label for Auromycin® (chlortetracycline), a commonly used feed additive in beef cattle, states "for the treatment of bacterial enteritis and pneumonia."[27] Other labeled uses for Auromycin® include "As an aid in control of active infection of anaplasmosis caused by *Anaplasma marginale* susceptible to chlortetracycline."[28] The claims are separate and distinct from the previous label claims, which stated, "increased rate of weight gain and improved feed efficiency."[29]

The FDA's implementation strategy in the transition was that of voluntary withdrawal of the production claims and reapplication for prevention and/or treatment claim by the sponsor (manufacturer). As of June 30, 2016 all sponsors affected by the FDA guidance for industry documents have agreed in writing to voluntarily withdraw their production or feed efficiency label claims.[30] By the date of implementation of the VFD rules on Jan. 1 2017 all labels for medically important antibiotics in feed additives and medicated feeds should be transitioned.

The veterinarian must know and follow the label on VFD drugs.

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[27] Aureomycin® is a trademark of Zoetis Services, LLC which is not affiliated with the development of this guide, the reference is used illustration purposes only.
https://www.zoetisus.com/products/beef/aureomycin_beef.aspx. Last Accessed Sept 15, 2106.
[28] *Id*.
[29] *Id.*
[30] See the FDA's Fifth Annual Progress report at
http://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm509403.htm. Last Accessed Sept 15, 2016.

The particular label claims of various VFD drugs will become very important for veterinarians to know and use. Extralabel use of drugs in food-producing animals is never allowed and is often the subject of FDA action against veterinarians.[31] The label will be the source of information regarding the indications for use, the maximal duration of feeding, any potential medicated combinations that could be fed, and any withdrawal times.[32] The veterinarian must write the VFD with pertinent labeling requirements in mind. The veterinarian will be viewed as the expert on the label claims when providing oversight to the antibiotic feeding process. Further, the veterinarian will often be involved with the explanation and edification of the label to the producer because a diagnosis is required and thus medical information is involved. A veterinarian that complies with label instructions will greatly reduce their liability risk. In summary, the veterinarian needs to thoroughly understand the labels for VFD drugs that are commonly used in their practice area, by their clients, producers, and feed distributers.

The VFD drugs' labels have specific species and indications on the label. The veterinarian issuing the VFD cannot deviate from the label regardless of whether the animal is intended for food production. The prohibition on extra-label use forbids use of the VFD drug in minor species not listed on the label, for major species in non-food production use, and for conditions not listed on the label.[33]

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[31] 21 CFR § 558.6(b)(3)(xiii) repeats the prohibition on extralabel use of medicated feeds found at 21 CFR 530.11(b) and 21 USC § 360b(a) which states, "the following specific extralabel uses are not permitted…Extralabel use of an approved new animal drug or human drug in or on an animal feed."
[32] 21 CFR § 558.6(a)(3)
[33] Animals not kept for food producing purposes, such as pot-bellied pigs, and pet chickens are specially identified as "always considered to be food-producing animals" in other another FDA Guidance for Industry Document, #230 at 4. Last accessed on Oct, 31, 2016.

The medical record should reflect the issuance of a VFD.

Another large impact on veterinarians is the recordkeeping requirements brought about by the new rules. The FDA's guidance is very detailed on both the information that must be recorded, and the method of recordkeeping of the actual VFD.[34] However, the FDA's publications are silent as to the medical recordkeeping requirements of the veterinarian and practice. Most states have statutes or regulations that require detailed written medical records to be kept by the veterinarian.[35] Practice to the standard of care almost always requires that a medical record be produced for each VCPR. The medical record is the veterinarian's main defense in later civil actions and/or state licensure actions. Additionally, the AVMA's Principles of Veterinary Medical Ethics, or the ethical requirements of the profession, state that records are an integral part of veterinary care.[36] Lastly, but of extreme importance, practices with good medical records tend to have more efficient communications among veterinarians and paraprofessionals, provide clearer communication to clients, provide better patient outcomes, and tend to have more value at practice transition than practices without adequate medical records.[37]

To issue a VFD a veterinarian must have "sufficient knowledge" of the production facility through "physical examination" or "visit of the facility."[38] How the veterinarian gained the knowledge to issue the VFD should be documented in the medical record.

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[34] 21 CFR § 558.6(b)(3)(i-xv).
[35] A 50 state survey of medical record retention, last accessed on Oct 31, 2016 at https://www.avma.org/Advocacy/StateAndLocal/Pages/sr-records-retention.aspx.
[36] Principle of Veterinary Medical Records V.b. Available at https://www.avma.org/kb/policies/pages/principles-of-veterinary-medical-ethics-of-the-avma.aspx. Last accessed Sept. 15, 2016.
[37] James F. Wilson, *Law and Ethics of the Veterinary Profession.* Priority Press, Yardley, PA. (1988).
[38] 21 CFR § 530.3(i)

The medical record should state a diagnosis for the herd that is consistent with label claims on the VFD drug.[39] Practically, it is impossible to definitely diagnosis every animal in a herd health setting. Some label claims will be made for preventative uses. Moreover, some diagnoses can only be made on post mortem examination. The FDA has been clear that a presumptive diagnosis, made with the veterinarian's clinical judgment is sufficient, but makes no requirement that the diagnosis be documented on the VFD form.[40]

The mechanism for enforcing the validity of the presumptive diagnosis, along with the veterinarian's clinical judgment, are highly necessary to meet the standard of care in a civil or state board action.[41] The medical record should support both the presumptive diagnosis and the veterinarian's clinical reasoning for issuing a VFD. Writing the record with the goal of indicating clearly how the veterinarian gained "sufficient knowledge" and how they arrived at a "presumptive diagnosis" for the label claim on the VFD drug will significantly decrease civil and board action induced liability to the veterinarian.

The medical record can incorporate the VFD and the information included within it by reference, so there is no need to repeat redundant information. Information not found on the VFD, but which is still relevant and important to include within the medical record, including the physical exam or facility findings,

[39] The federal VCPR states, "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)." 21 CFR § 530.3(i)2.

[40] *Id*.

[41] The standard of care is framed as a question in most jurisdictions asking, "Did the veterinarian act as a ordinary and prudent practitioner in the situation?" A general practitioner will be held to the standard of care as other ordinary and prudent general practitioners and a specialist will be held to the standard of care of other similar specialist. For example a Diplomate of the American College of Swine veterinarians will be held to the standard of care of other Diplomates.

pertinent information regarding the history, husbandry and intended use of the animals, the presumptive or definitive diagnosis and any other relevant client communication regarding the animals. The Subjective, Objective, Assessment, Plan (SOAP) manner of writing medical records could be slightly modified to capture all pertinent aspects of the document, but by using a herd health approach instead of a individual patient approach.

The identification and location of the animals to be fed the VFD will pose logistical concerns for the veterinarian. Many veterinary hospitals do not currently use software packages or paper filing systems that allow different parties for the client and owner.[42] Data input fields are often not available to allow the practice to capture different locations. For purposes of filing and searchability, the practice should standardize the manner of data entry to input the herd health and VFD data. A medical recordkeeping system of standardized nomenclature of herds receiving VFD drugs could be developed by the practice. Since the herds don't have given names like individual animals, the name of the patient in the medical record is created by the practice personnel. For example, a herd health system of recordkeeping could be analogous to the animal(s) identification on the VFD. The name field could state "50 Angus heifers received into pen 11C on 4-1-17," then pertinent medical information could be entered. This name could also abbreviated with a standardized practice naming convention to "50 Ang H 11C 4.1.17."

[42] Many veterinary medical records for herd health currently identify the owner's herd as "cattle" or "swine" when the animals aren't uniquely identified. The medical record will often then follow medications dispensed chronologically and individually treated animals are identified when needed. This will pose problems when the different VFDs with different expiration dates are issued for certain lots of animals at the same time, and differing presumptive diagnoses are entered should the need arise to extract information about a specific VFD for specific animals.

Practices currently utilizing handwritten records should strongly consider converting to electronic medical records (eMRs) for animals being fed VFD drugs, due to the recordkeeping requirements for large producers and practices issuing large numbers of VFDs. Cloud-based recordkeeping systems that are mobile and automatically updated via internet connection make eMR systems appealing to ambulatory practitioners. Tablet-based systems are becoming more functional and these technologies could become a labor saving technology for mobile food animal veterinarians issuing even moderate numbers of VFDs.

Electronic transmission and storage of the VFD is allowed.

Another time and labor saving technology that will improve the efficiency of the VFD process for veterinarians and their offices is the electronic transmission of the VFD. The VFD rules clearly state that the veterinarian is responsible for delivery to the feed mill or distributer.[43] The entire form can be electronic; even the signature of the issuing veterinarian.[44] Paradoxically, VFDs that are emailed are not considered "electronic VFDs" but are considered to be transmitted electronically.[45] True electronic VFDs are generated and transmitted via the internet generally by a third party service that is neither the veterinarian nor the feed distributer.[46] The most simplistic version of the transmission and storage of a written VFD is on an internet-based email or server system.

[43] The rule states specifically, "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." 21 CFR § 588.6 (b)(ii)(8).
[44] 21 CFR § 558.6(b)(3)
[45] See Guidance for Industry Document #120 (D.4.) at page 13.
[46] A true electronic VFD is required to be 21 CFR 11 compliant. This regulation lays out the verification and security requirements for a third party processor.

The VFD must be retained by the veterinarian for 2 years, either in its electronic or paper form. The VFD rules do not specify the location or security of the VFD. The most simplistic and practical version of transmission and storage would be an electronic tablet with a fillable VFD form.[47] The form could then be signed by the veterinarian.[48] An email of the VFD could be emailed to the producer and the distributer and carbon copied to the veterinarian before leaving the facility. The carbon copy (cc) version could then be attached to the producer's electronic medical record to be stored electronically and in a folder within the email service.

The VFD must contain a physical location.

The VFD rules require that the street address, GPS coordinates, or physical characteristics such as pen, barn, tank or other distinguishing characteristics be listed on the VFD. The FDA states that it understands that animals may come and go from lots of animals and animals may move to other locations. Therefore, it is acceptable to list multiple locations on the VFD.[49] This exception is caveated by the requirement that the veterinarian needs to be licensed in each state and the feed for one VFD must come from a single manufacturer.

There is no standardized VFD form, but the AVMA, the FDA, and drug manufacturers have provided examples.

[47] Several "stock" forms will be required for various different feeding scenarios such as
[48] To be 21 CFR 11 compliant a veterinarian needs to make a one-time certification in paper form to the FDA and signed with a traditional handwritten signature. This letter needs to be mailed to the Office of Regional Operations (HFC-100), 5600 Fishers Lane, Rockville, MD 20857. This certification needs to state that the signatures are intended to be the legally binding equivalent of traditional handwritten signatures.
[49] See FDA Guidance For Industry document #120 at 3.

The veterinarian can choose to create their own paper VFD form as long as the regulatory requirements are met.[50] The FDA has distributed an example that can be used or modified.[51]

The entire VFD form creating process could be completed online, with electronic transmission and storage online. The veterinarian's signature could be electronic, eliminating the need for printing and scanning of the document.[52] For efficiency, time and cost savings, and reduction of errors, it is suggested that veterinary practices streamline their process with the use of technology. Practically, the less time that a veterinarian spends writing and transmitting the VFD, the more efficient and productive they can be in other areas of practice. A more efficient process will aid the veterinary practice in maintaining profitability while complying with the VFD rules.

The veterinarian can charge the client for forming the VCPR and issuing the VFD, but they will need to become as efficient as possible.

Food animal veterinary practice is labor intensive, time consuming, and producers are cost sensitive. Practically, it will be difficult for a veterinarian to charge appropriately for the time and travel costs to visit and examine animals or inspect facilities. For a veterinarian to establish a presumptive or definitive diagnosis will take time that was not previously required when medically important antibiotics could be obtained over the counter. Additional communication with the client will be needed to establish the approximate number of animals, the intended

[50] See Guidance for Industry Document #230. Attachment 3.
[51] See Attachment 7, which is replicated from the FDA example found in Guidance for Industry Document #233, pgs. 13,14, and 15.
[52] See page 15 for electronic VFD requirements.

use of the animals, and the expiration of the VFD. Client education will be a major component of these changes. The practicing veterinarian will have a large initial time outlay in order to gain the knowledge to issue VFDs that are compliant for labeling, combination drug usage, withdrawal times and cautionary statements. Lastly, the transmission and storage of the VFD and the increased medical recordkeeping implications will be time-consuming for the veterinarian and paraprofessionals. Producers not currently budgeting increased veterinary fees for the increased veterinary oversight will be price sensitive and at times could become frustrated with the veterinary practice for charging for the veterinarian's time. Still though, it will be difficult to properly charge for the veterinarian's time, unless the practice is efficient and streamlined in the research, writing, transmission and storage of the VFD.

Communicating with producers every time a facility visit is made about the possibility of a future VFD need could reduce single-purpose visits made to issue a VFD. Also, coordinating and combining visits to distinct production facilities in rural areas could decrease drive time and lower costs of implementation. Training paraprofessionals to obtain standard history, perform data entry, and provide common client education could limit veterinarian input time.

Practices that are in heavy food animal production regions may consider hosting client education workshops or events. Handing out brochures, client information literature and directing clients to online information may provide

additional time savings.[53] Veterinarians will certainly want to work with local feed mills (distributers), retailers, and large production facilities to streamline and standardize their communications and VFD transmission.

A producer can mix medicated feed on the farm and a veterinary hospital can sell medicated articles or feed.

Many animal producers mix feed on their facility for immediate feeding, using bulk-quantity medicated crumbles or mix.[54] These producers currently buy the drug in bulk from a retailer/distributer. After implementation of the VFD rule, the producer will still be able to mix medicated feed as long as the labeling and VFD instructions are met.

The veterinary practice can sell medicated Type A (medicated articles) or Type B (mineral/supplement mixes) directly to producers for use on their facility. To do this however, the veterinary practice would need to submit a one-time letter of distribution to the FDA and also ensure that each producer has valid VFD before purchase.[55] If the veterinary practice were to sell to other distributors or entities then mixing or selling feeds for other producers, then the veterinary practice would need to keep a "acknowledgement letter" from the buyer of the feed.[56]

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[53] The National Agriculture Law Center will make further multimedia information, tailored for producers and distributers available.

[54] Type A medicated articles are used to manufacture another Type A or for production of type B or C medicated feeds. Type B medicated feeds contain vitamins or minerals and are can be used for the manufacture of other medicated feeds and Type C medicated feeds are completed feeds or could be used as top dressing.

[55] Guidance for Industry Document #120 at page 20.

[56] 21 CFR § 558.3(b)(11) states that "An acknowledgement letter must be provided either in hardcopy or through electronic media, and must affirm: (1) that the distributor will not ship such VFD feed to an animal production facility that does not have a VFD; (2) that the distributor will not ship such VFD feed to another distributor without receiving a similar written acknowledgment letter; and (3) that the distributor has complied with the distributor notification requirements in 21 CFR 558.6(c)(5)."

To purchase the VFD drug, the retailer will need to maintain a letter of distribution on file from the producer and a valid VFD for the drug to be purchased.[57]

In conclusion, the new VFD rules represent some of the largest regulatory changes to food animal veterinary practice in decades. Veterinarians practicing in production and mixed animal settings need to understand the rules, guidance documents, and VFD drug labels. Of particular importance for veterinarians is determining how to establish a valid VCPR with the sufficient knowledge needed to write the VFD. Further, veterinarians should be diligent in creating thorough medical records that document the presumptive diagnosis and how the veterinarian found a need for a VFD drug. Veterinarians could take advantage of increased oversight to provide value for their services to clients. Lastly, veterinarians and their practice's offices should work to become as efficient as possible to write, transmit and store VFDs in order to remain profitable during the upcoming changes.

[57] The process to obtain a letter of distribution can be found at (21 CFR 558.6(c)(5)) and also within Guidance for Industry Document #120 at pg. 19. In summary, the distributor's complete name and business address, the distributor's signature or the signature of the distributor's authorized agent, and the date the notification was signed. The letter can be mailed or faxed to: Food and Drug Administration, Center for Veterinary Medicine, Division of Animal Feeds (HFV-220), 7519 Standish Pl., Rockville, MD 20855, FAX: 240-453-6882. Anytime the distributer moves, has a change in ownership or name, it must update the FDA within 30 days.

Drugs Transitioning from Over-the-Counter (OTC) to Veterinary Feed Directive (VFD) Status

Upon completion of their voluntary transition from OTC to VFD, all feed uses of the following drugs, alone and in a combination, will require a VFD as of January 1, 2017, except in cases where a sponsor chooses to voluntarily withdraw the drug application:

Drugs Transitioning From OTC to VFD Status

Established drug name	Examples of proprietary drug name(s) [$]
chlortetracycline (CTC)	Aureomycin, CLTC, CTC, Chloratet, Chlorachel, ChlorMax, Chlortetracycline, Deracin, Inchlor, Pennchlor, Pfichlor
chlortetracycline/sulfamethazine*	Aureo S, Aureomix S, Pennchlor S
chlortetracycline/sulfamethazine/penicillin*	Aureomix 500, Chlorachel/Pficlor SP, Pennchlor SP, ChlorMax SP
hygromycin B	Hygromix
lincomycin	Lincomix
oxytetracycline (OTC)	TM, OXTC, Oxytetracycline, Pennox, Terramycin
oxytetracycline/neomycin*	Neo-Oxy, Neo-Terramycin
penicillin[+]	Penicillin, Penicillin G Procaine
sulfadimethoxine/ormetoprim*	Rofenaid, Romet
tylosin	Tylan, Tylosin, Tylovet
tylosin/sulfamethazine*	Tylan Sulfa G, Tylan Plus Sulfa G, Tylosin Plus Sulfamethazine
virginiamycin	Stafac, Virginiamycin, V-Max

Note: apramycin, erythromycin, neomycin (alone), oleandomycin[+], sulfamerazine, and sulfaquinoxaline are also approved for use in feed and are expected to transition to VFD status, but are not marketed at this time. If they return to the market after January 1, 2017, they will require a VFD.

[$]Type A medicated articles used to manufacture medicated feed, all products may not be marketed at this time

*Fixed-ratio, combination drug

[+]Currently only approved for production uses

Current VFD Drugs

Established drug name	Proprietary drug name(s) [$]
avilamycin	Kavault
florfenicol	Aquaflor, Nuflor
tilmicosin	Pulmotil, Tilmovet
tylvalosin	Aivlosin

[$]Type A medicated articles used to manufacture medicated feed

This information is up-to-date as of August 8, 2016. As the industry transitions, CVM anticipates additional changes during the coming months to this information. Please check the link below for the most recent updates:
http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/ucm071807.htm

#209

Guidance for Industry

The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals

Submit comments on this guidance at any time. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. Submit electronic comments on the guidance at http://www.regulations.gov. All written comments should be identified with the Docket No. FDA-2010-D-0094.

For further information regarding this document, contact William T. Flynn, Center for Veterinary Medicine (HFV-1), Food and Drug Administration, 7519 Standish Place, Rockville, MD 20855, 240-276-9084. E-mail: william.flynn@fda.hhs.gov.

Additional copies of this guidance document may be requested from the Communications Staff (HFV-12), Center for Veterinary Medicine, Food and Drug Administration, 7519 Standish Place, Rockville, MD 20855, and may be viewed on the Internet at either http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/default.htm or http://www.regulations.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine
April 13, 2012

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The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals

This guidance represents the Food and Drug Administration's (FDA) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the number listed on the previous page of this guidance.

I. Executive Summary

Antimicrobial drugs have been widely used in human and veterinary medicine for more than 50 years, with tremendous benefits to both human and animal health. The development of resistance to this important class of drugs, and the resulting loss of their effectiveness as antimicrobial therapies, poses a serious public health threat. Misuse and overuse of antimicrobial drugs creates selective evolutionary pressure that enables antimicrobial resistant bacteria to increase in numbers more rapidly than antimicrobial susceptible bacteria and thus increases the opportunity for individuals to become infected by resistant bacteria. Because antimicrobial drug use contributes to the emergence of drug resistant organisms, these important drugs must be used judiciously in both animal and human medicine to slow the development of resistance. Efforts have been made to promote the judicious use of these drugs in humans (see http://www.cdc.gov/getsmart/index.html) as well as in animals (see http://www.avma.org/issues/default.asp). Using these drugs judiciously means that unnecessary or inappropriate use should be avoided. The focus of this document is on the use of medically important antimicrobial drugs[1] in food-producing animals. Based on a consideration of the available scientific information, FDA is providing a framework for the voluntary adoption of practices to ensure the appropriate or judicious use of medically important antimicrobial drugs in food-producing animals. This framework includes the principles of phasing in such measures as 1) limiting medically important antimicrobial drugs to uses in food-producing animals that are considered necessary for assuring animal health; and 2) limiting such drugs to uses in food-producing animals that include veterinary oversight or consultation. Developing strategies for reducing antimicrobial resistance is critically important for protecting both public and animal health. Collaboration involving the public, the public health, animal health, and animal agriculture communities on the development and implementation of such strategies is needed to assure that the public health is protected while also assuring that such strategies are feasible and that the health needs of animals are addressed.

[1] The term "medically important antimicrobial drugs" generally refers to antimicrobial drugs that are important for therapeutic use in humans.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word "should" in Agency guidances means that something is suggested or recommended, but not required.

II. Introduction

Antimicrobial resistance[2], and the resulting failure of antimicrobial therapies in humans, is a mounting public health problem of global significance. This phenomenon is driven by many factors including the use of antimicrobial drugs in both humans and animals. In regard to animal use, this document addresses the use of medically important antimicrobial drugs in food-producing animals for production or growth-enhancing purposes. These uses, referred to as production[3] uses throughout this document, are typically administered through the feed or water on a herd- or flock-wide basis and are approved for such uses as increasing rate of weight gain or improving feed efficiency. Unlike other uses of these drugs in animals (e.g., for the treatment, control, and prevention of disease), these "production uses" are not intended to manage a specific disease that may be ongoing or at risk of occurring, but rather are expressly indicated and used for the purpose of enhancing the production of animal-derived products (e.g., increasing rate of weight gain or improving feed efficiency). This document summarizes some of the key reports and scientific literature related to the use of antimicrobial drugs in animal agriculture and outlines FDA's current thinking on strategies for assuring that medically important antimicrobial drugs are used judiciously in food-producing animals in order to help minimize antimicrobial resistance development. In finalizing this guidance, FDA has considered comments that were submitted to the docket, and other relevant information. If you have additional relevant information, please submit it to the docket at any time. We are particularly interested in any new information regarding the use of medically important antimicrobials in food-producing animals and its impact on the development of drug-resistant bacteria.

[2] The term "antimicrobial" refers broadly to drugs with activity against a variety of microorganisms including bacteria, viruses, fungi, and parasites. Antimicrobial drugs that have specific activity against bacteria are referred to as antibacterial or antibiotic drugs. However, the broader term "antimicrobial," commonly used in reference to drugs with activity against bacteria, is used in this document interchangeably with the terms antibacterial or antibiotic. Antimicrobial resistance is the ability of bacteria or other microbes to resist the effects of a drug. Antimicrobial resistance, as it relates to bacterial organisms, occurs when bacteria change in some way that reduces or eliminates the effectiveness of drugs, chemicals, or other agents designed to treat bacterial infections.

[3] Production uses are also referred to as "nontherapeutic" or "subtherapeutic" uses, terms that we believe lack sufficient clarity.

III. Key Reports and Peer-Reviewed Scientific Literature on the Issue

Questions regarding the use of antimicrobial drugs in food-producing animals have been raised and debated for many years. A variety of recognized international, governmental, and professional organizations have studied the issue. We have briefly summarized below the findings and recommendations from some of the notable reports that have addressed this issue over the past 40 years. These reports provide context to FDA's current thinking on this issue, and highlight the longstanding concerns that have been the subject of discussion in the scientific community as a whole.

We have also provided a list below of some of the more recent primary scientific literature that FDA has considered. This is not intended to represent an exhaustive summary of the scientific literature, but rather to highlight some of the more recent scientific research related to the use of antimicrobial drugs in animal agriculture and the impact of such use on antimicrobial resistance. We acknowledge that a significant body of scientific information exists, including some information that may present equivocal findings or contrary views.

Unless otherwise indicated, the page numbers cited in this section refer to the relevant page numbers in the referenced report. A complete list of the reports summarized in this section is provided at Section IX of this document.

Reports Prepared by Various International, Governmental, and Professional Organizations

1969 Report of the Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine

In July 1968, a Joint Committee was established in the United Kingdom to obtain information regarding the use of antibiotics in animal husbandry and veterinary medicine, particularly with respect to antibiotic resistance. This report, often referred to as the "Swann Report," was presented to Parliament in November 1969 by the Secretary of State for Social Services, the Secretary of State for Scotland, the Minister of Agriculture, Fisheries and Food, and the Secretary of State for Wales. The report concluded that the administration of antimicrobials to food-producing animals, particularly at subtherapeutic levels, poses a hazard to human and animal health.

The report stated, "It is clear that there has been a dramatic increase over the years in the numbers of strains of enteric bacteria of animal origin which show resistance to one or more antibiotics. Further, these resistant strains are able to transmit this resistance to other bacteria. This resistance has resulted from the use of antibiotics for growth promotion and other purposes in farm livestock" (*Ref. 1,* p. 60). The report also noted, "There is ample and incontrovertible evidence to show that man may commonly ingest enteric bacteria of animal origin" (*Ref. 1,* p. 60).

The report provided a number of recommendations including that only antimicrobials which "have little or no application as therapeutic agents in man or animals and will not impair the efficacy of a prescribed therapeutic drug or drugs through the development of resistant strains of organisms" should be used without prescription in animal feed (*Ref. 1*, p. 61). Furthermore, the report concluded that antimicrobials used for therapeutic purposes in food-producing animals should remain available but only under veterinary supervision.

1970 FDA Task Force Report, "The Use of Antibiotics in Animal Feed"

In April 1970, FDA established a task force of scientists to undertake a comprehensive review of the use of antibiotics in animal feed *(Ref. 2)*. The task force included ten specialists on infectious diseases and animal science from FDA, the National Institutes of Health, the U.S. Department of Agriculture, and the Centers for Disease Control and Prevention, as well as five consultants from universities and industry.

This task force acknowledged that the understanding at the time it conducted its study was that the use of antimicrobials in food-producing animals, especially in subtherapeutic amounts, was associated with the development of resistant bacteria, and that treated animals might serve as a reservoir of antimicrobial-resistant pathogens that could produce human disease.

The recommendations of the Task Force included that antimicrobial drugs used in human clinical medicine that failed to meet certain guidelines established by the Task Force should be prohibited from growth promotion and any subtherapeutic use in food-producing animals by certain dates. Furthermore, those antimicrobials that failed to meet the guidelines should be limited to short-term therapeutic use and use only by a veterinarian or on a veterinarian's prescription.

As a consequence of the 1970 Task Force report, requirements for data to address microbiological safety concerns for subtherapeutic uses of antimicrobials in food-producing animals were outlined in the Code of Federal Regulations (21 CFR 558.15). Sponsors of antibiotic products administered in animal feed for subtherapeutic purposes were required to submit study results demonstrating that their product did not promote bacterial drug resistance. Depending on the class of drug, sponsors were required to submit all information to the agency on the impact of their drug on enteric salmonella in treated animals by specific dates.

1980 National Academy of Sciences Report, "The Effects on Human Health of Subtherapeutic Use of Antimicrobial Drugs in Animal Feeds"

In 1977, FDA proposed to withdraw the new animal drug approvals for subtherapeutic uses of penicillin and tetracyclines in animal feed on the ground that evidence showed that these drugs, when used for such purposes in animal feed, had not been shown to be safe. These two drugs were chosen because of their importance in human medicine. The proposal was criticized because, at that time, there was not adequate epidemiological evidence (or only just-emerging evidence) to show that drug-resistant

bacteria of animal origin were commonly transmitted to humans and caused serious illness. Subsequently, Congress directed FDA to conduct further studies related to the use of antimicrobials in animal feed and to hold in abeyance the implementation of the proposed antimicrobial withdrawal actions pending the outcome of these studies.

In accordance with Congress' directive to conduct further studies, FDA contracted with the National Academy of Science to conduct a study of the safety issues related to the use of antimicrobials in animal feed. In particular, FDA asked the National Academy of Science to: 1) study the human health effects of the subtherapeutic use of penicillin and tetracycline in animal feed; 2) review and analyze published and unpublished data relevant to assessing human health consequences of such use; 3) assess the scientific feasibility of additional epidemiological studies; and (4) make recommendations about additional research needed.

The National Academy of Sciences issued a study report in 1980. The study report concluded that a very limited amount of epidemiological research had been completed on either the subtherapeutic or therapeutic use of antimicrobials in animal feed. According to the study report, much of the information available on the subject involved "poorly controlled studies of small numbers of subjects for brief periods" (*Ref. 3*, p. 52). Based on a consideration of available evidence, the report concluded that existing data could neither prove nor disprove the postulated hazards to human health from subtherapeutic antimicrobial use in animal feed. However, the report cautioned that "The lack of data linking human illness with subtherapeutic levels of antimicrobials must not be equated with proof that the proposed hazards do not exist. The research necessary to establish and measure a definitive risk has not been conducted and, indeed, may not be possible" (*Ref. 3*, p. 53).

1984 Seattle-King County Study: "Surveillance of the Flow of Salmonella and Campylobacter in a Community"

As noted above, Congress directed FDA to hold in abeyance any implementation of the proposed withdrawal of new animal drug approvals for the subtherapeutic uses of penicillin and tetracyclines in animal feed, pending completion of additional studies related to the use of antimicrobials in animal feed. Therefore, in addition to the National Academy of Sciences study described above, the FDA also contracted with the Seattle-King County Health Department to complete a study intended to provide additional information regarding potential public health concerns regarding the use of antimicrobial drugs in animal feed. Under the contract, the Communicable Disease Control Section of the Seattle-King County Health Department was tasked with studying the relationship between the occurrence of Salmonella spp. (*Salmonella*) and Campylobacter jejuni (*C. jejuni*) in foods of animal origin and the occurrence of human illness caused by those two organisms. These two organisms, *Salmonella* and *C. jejuni*, were chosen to serve as models to estimate the flow of potentially pathogenic bacteria from animals to man through the food chain. The study involved a two-pronged surveillance system that included sampling of retail meats over a 20 month period and simultaneous investigation of *Salmonella* and *C. jejuni* enteritis cases in humans. Bacterial isolates from food and human cases were subjected to

antibiotic susceptibility testing, plasmid analysis, and serotyping. In 1984, the Seattle-King County Health Department prepared a report summarizing the results of the study. The 1984 study report found that *C. jejuni* was a more common cause of enteritis than *Salmonella*. Also, it concluded that *C. jejuni* "does appear to flow from chickens to man via consumption of poultry products" (*Ref. 4*, p. 3). The report stated, "isolates from human cases and those from retail poultry had similar antibiotic susceptibility patterns, including prevalence of 29.7% and 32.8%, respectively, for tetracycline resistance, which was found to be plasmid-mediated" (*Ref. 4*, p. 3).

1988 Institute of Medicine (IOM) Report: "Human Health Risks with the Subtherapeutic Use of Penicillin or Tetracyclines in Animal Feed"

In 1987, FDA asked the IOM to conduct an independent review of the human health risks associated with the subtherapeutic use of penicillin and tetracycline in animal feed. IOM established a committee and directed it to perform "a quantitative risk assessment" of these human health consequences and to "assess the adequacy of the existing human health data and use such data to arrive at an estimate of risk" (*Ref. 5*, p. iii). If quantification of human health risks was not possible due to inadequate data, the Committee was to evaluate the scientific information that had become available since the 1980 National Academy of Science report cited above.

The Committee developed a risk-analysis model, using data only on *Salmonella* infections that resulted in human death. However, the Committee was unable to find a substantial body of direct evidence demonstrating that the subtherapeutic use of penicillin or tetracycline in animal feed posed a human health hazard. Nonetheless, the Committee's 1988 report found a considerable body of indirect evidence implicating both subtherapeutic and therapeutic use of antimicrobials as a potential human health hazard. The Committee also strongly recommended further study of the issue.

1997 World Health Organization (WHO) Report, "The Medical Impact of Antimicrobial Use in Food Animals"

In October 1997, the WHO convened a meeting of experts to examine the question of whether the use of antimicrobials in livestock production, including through use in animal feed, contributes to the escalation of antimicrobial resistance in humans. The findings of the meeting, which were summarized in a report, included the conclusion that all uses of antimicrobials lead to the selection of resistant forms of bacteria. Furthermore, the report stated that "low-level, long-term exposure to antimicrobials may have greater selective potential than short-term, full-dose therapeutic use" (*Ref. 6*, p. 5). The report found that the selection of resistant bacteria has adverse consequences for preventing and treating disease in humans, animals, and plants.

The WHO expert committee recommended that the use of antimicrobial drugs for growth promotion in animals be terminated if these drugs are also prescribed for use as anti-infective agents in human medicine or if they are known to induce cross-resistance to antimicrobials used for human medical therapy. The Committee also recommended the

development of a systematic approach towards replacing growth-promoting antimicrobials with safer non-antimicrobial alternatives. The expert committee called for enhanced monitoring of resistance among isolates of enteric bacteria from food animals and food of animal origin. In addition, the Committee recommended managing risk at the primary production level through measures that promote the prudent use of antimicrobials, including enforcement of relevant laws pertaining to antimicrobial use, education for prescribers and producers, and requiring that use of antimicrobials for treatment of infections in animals be prescribed by veterinarians.

1999 National Research Council (NRC) Report: "The Use of Drugs in Food Animals – Benefits and Risks"

The Panel on Animal Health, Food Safety, and Public Health, jointly sponsored by the NRC's Board on Agriculture and IOM's Food and Nutrition Board, initiated a project to review the issues and relevant information regarding the use of drugs in food-producing animals and to make recommendations about such use. The panel convened the Committee on Drug Use in Food Animals to examine the benefits and risks associated with drug use in food-producing animals and to prepare a report and make recommendations.

The Committee's 1999 report included a review of the issues related to antibiotic use in food-producing animals and provided a number of recommendations. The report recommended establishing national databases to support scientific process and policy development for the approval and use of antibiotics in food-producing animals. The report also recommended that FDA use interdisciplinary panels of experts so that "further development and use of antibiotics in both human and animal medicine have oversight by an interdisciplinary panel of experts composed of representatives of the veterinary and animal health industry, the human medicine community, consumer advocacy groups, the animal production industry, and the regulatory agencies" (*Ref. 7*, p. 11).

1999 United States Government Accountability Office (GAO) Report – "Food Safety: The Agricultural Use of Antibiotics and Its Implications for Human Health"

In response to a request from Congress, the GAO initiated a study in May 1998 to examine: "1) how antibiotics are used in agriculture and the implications of that use for human health; 2) federal roles and responsibilities for overseeing the use of antibiotics in agriculture; and 3) issues surrounding the debate over whether to further regulate or restrict the use of antibiotics in agriculture" (*Ref. 8*, p. 1).

In its study report, dated April 1999, GAO concluded that although research has linked the use of antibiotics in agriculture to the emergence of resistant foodborne pathogens, "there are no current comprehensive estimates of the extent to which antibiotic-resistance strains have resulted in illness and deaths" (*Ref. 8*, p. 1). GAO concluded that the debate over whether antibiotic use should be restricted in agriculture centers on the risk antibiotics pose to human health relative to their benefits to agriculture. The GAO report recommended that "the departments of Agriculture and Health and Human Services work

together to develop and implement a plan with specific goals, time frames and resources needed for determining the safe use of antibiotics in agriculture."

1999 European Commission Report, "Opinion of the Scientific Steering Committee on Antimicrobial Resistance"

Due to the public and animal health concerns associated with the increasing rate of antimicrobial resistance development, the European Commission, Directorate-General XXIV, asked that organization's Scientific Steering Committee to "scientifically evaluate the current position regarding the prevalence and development of antimicrobial resistance, examine its implications for human and animal health, particularly with regard to the development and management of infections" (*Ref. 9*, p. 7).

The Committee's report concluded that actions should be taken promptly to reduce the overall use of antimicrobials. Four primary recommendations were forwarded: (1) antimicrobial drugs should be used prudently; (2) infections should be prevented and resistant organisms contained; (3) research for new modalities of prevention and treatment of infections should be undertaken; and (4) the effects of such interventions should be monitored and evaluated.

2000 World Health Organization (WHO) Expert Consultation: "WHO Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food"

The Food and Agriculture Organization of the United Nations (FAO) and the World Organization for Animal Health (OIE) participated in the June 2000 WHO expert consultation, the purpose of which was to develop global principles for minimizing the negative public health impact associated with the use of antimicrobial agents in food-producing animals while providing for their safe and effective use in veterinary medicine *(Ref. 10)*.

The principles were part of a comprehensive WHO global strategy for the containment of antimicrobial resistance and provided a framework of recommendations to reduce the overuse and misuse of antimicrobials in food-producing animals for the protection of human health. The principles strengthened and endorsed earlier WHO recommendations such as the need to terminate the use of antimicrobial growth promoters pending comprehensive human health safety evaluations, the need to ensure that all antimicrobials for animal use are only supplied through authorized outlets (e.g., by veterinary prescription), and the need to establish surveillance systems on antimicrobial drug consumption.

2003 Report, "Joint FAO/OIE/WHO Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance: Scientific assessment"

In December 2003, the Food and Agriculture Organization of the United Nations (FAO), the World Organization for Animal Health (OIE), and the World Health Organization (WHO) convened a workshop to "perform a scientific assessment of the antimicrobial resistance risks arising from non-human usage of antimicrobials and to

formulate recommendations and options for future risk management actions to be considered by the Codex Alimentarius Commission (Codex) and OIE" (*Ref. 11*, p. 1).

The expert panel's findings from the workshop were documented in a report which contained a number of conclusions, including: 1) "there is clear evidence of adverse human health consequences due to resistant organisms resulting from non-human usage of antimicrobials;" 2) "the amount and pattern of non-human usage of antimicrobials impact the occurrence of resistant bacteria in animals and on food commodities and thereby human exposure to these resistant bacteria;" 3) "the foodborne route is the major transmission pathway for resistant bacteria and resistance genes from food animals to humans, but other routes of transmission exist;" and 4) the "consequences of antimicrobial resistance are particularly severe when pathogens are resistant to antimicrobials critically important in humans" (*Ref. 11*, p. 1).

The expert panel recommended that WHO appoint a group of experts to define which antimicrobials are considered critically important in humans. In addition, the panel commented on the need to further develop risk assessment approaches that adequately address the broad range of potential human health impacts and encouraged OIE to continue its work on risk analysis in coordination with FAO and WHO. Finally, the panel recommended that Codex collaborate with OIE to define a more efficient risk management system for addressing the risks.

2003 Institute of Medicine (IOM) Report, "Microbial Threats to Health: Emergence, Detection and Response"

The Committee on Emerging Microbial Threats to Health in the 21st Century was charged by the IOM to "review the current state of knowledge on the emergence of infectious diseases; assess the capacity of the United States to detect and respond to microbial threats to public health; and identify potential challenges and opportunities for public health actions, both global and domestic, to strengthen capabilities in prevention, detection, and response" (*Ref. 12*, p. 3).

The Committee's report discussed thirteen factors[4] that account for the emergence of new or enhanced microbial threats. The report noted "the convergence of any number of factors can create an environment where infectious diseases can emerge…" (*Ref. 12*, p. 4). In addition, the Committee provided a number of recommended actions for responding to the increasing infectious disease rates prompted by these emergence factors. One of the recommendations was to "more finely target the use of antimicrobials" including expanding efforts to decrease the inappropriate use of antimicrobials in human medicine (*Ref. 12*, p. 6). In addition, the committee recommended that "FDA ban the use of

[4] The thirteen factors included 1) microbial adaptation and change, 2) human vulnerability, 3) climate and weather, 4) changing ecosystems, 5) economic development and land use, 6) human demographics and behavior, 7) technology and industry, 8) international travel and commerce, 9) breakdown of public health measures, 10) poverty and social inequality, 11) war and famine, 12) lack of political will, and 13) intent to harm.

antimicrobials for growth promotion in animals if those classes of antimicrobials are also used in humans" (*Ref. 12*, p. 15).

2004 Report, "Second Joint FAO/OIE/WHO Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance: Management Options"

As summarized above, a preliminary scientific assessment of the antimicrobial resistance risks arising from non-human usage of antimicrobials was conducted by the first Joint Expert Workshop on Non-Human Antimicrobial Usage in December 2003 in Geneva *(Ref. 13)*. The outcome of the first workshop, plus other relevant information, formed the basis for consideration by this second workshop. The report of this second workshop included suggestions to Codex, FAO, WHO, and OIE for moving forward on the issue.

Some of the key conclusions and recommendations in the report included: 1) the risks associated with non-human antimicrobial use and antimicrobial resistance should be part of human safety assessments for regulatory decisions relating to veterinary antimicrobials, 2) the concept of "critically-important" classes of antimicrobials for humans should be developed by WHO, 3) good agricultural practices can reduce the necessity for antimicrobials, 4) there is a need for capacity building and networking to help implement antimicrobial resistance surveillance systems in various countries, and 5) a Codex/OIE Task Force should be established to develop risk management options for antimicrobial resistance related to non-human use of antimicrobials.

2004 United States Government Accountability Office (GAO) Report – "Antibiotic Resistance: Federal Agencies Need to Better Focus Efforts to Address Risks to Humans from Antibiotic Use in Animals"

In response to a request from Congress, GAO initiated a study in May 2003 to "examine 1) scientific evidence on the transference of antibiotic resistance from animals to humans and extent of potential harm to human health, 2) agencies' efforts to assess and address these risks, 3) the types of data needed to support research on these risks and extent to which the agencies collect these data, 4) use of antibiotics in animals in the United States compared with its key agricultural trading partners and competitors, and 5) information on how use has affected trade" (*Ref. 14*, p. 3).

In its study report, dated April 2004, GAO concluded that antibiotic-resistant bacteria have been transferred from animals to humans. GAO also stated that many of the studies reviewed as part of GAO's research found that this transference from animals to humans poses significant risks for human health. According to GAO's findings, studies have shown two types of evidence related to the transfer of antibiotic-resistant bacteria from animals to humans. First, some studies have provided evidence of associations between changes in antibiotic use in animals and resistance to antibiotics in human bacteria. For example, researchers have found that antibiotic-resistant *Escherichia coli* (*E. coli*) and *Campylobacter* increased in humans as use of the antibiotics increased in animals.

Second, GAO concluded that studies that have examined the genetic makeup of the bacteria have provided stronger scientific evidence that antibiotic-resistant *Campylobacter*

and *Salmonella* bacteria are transferred from animals to humans. In those studies, strains of antibiotic-resistant bacteria infecting humans were indistinguishable from those found in animals, leading researchers to conclude that the animals were the source of human infection.

The GAO report noted that researchers disagree about the extent of the human health risk caused by this transference. According to the report, "many researchers contend that antibiotic use in animals poses significant risk for human health." The GAO report also noted that "a small number of studies contend that the health risks of the transference are minimal" (*Ref. 14*, p. 23).

GAO recommended that "the Commissioner of FDA expedite FDA's risk assessments of the antibiotics used in animals that the agency has identified as critically important to human health to determine if action is necessary to restrict or prohibit animal uses in order to safeguard human health" (*Ref. 14*, p. 48). GAO also recommended that the Secretaries of Agriculture and of Health and Human Services "jointly develop and implement a plan for collecting data on antibiotic use in animals..." (*Ref. 14*, p. 48).

The Department of Health and Human Services (HHS) reviewed and subsequently responded to the 2004 GAO Report on Antibiotic Resistance. In its response, HHS cited 11 additional supporting studies not included in the GAO report (See End Note)[i], and provided the following comments:

"The draft report presents or refers to significant and growing evidence demonstrating the human health consequences of drug resistant infections related to antibiotic use in agriculture." "These [11 additional] studies, along with those cited in the GAO report, all demonstrate a relationship between the use of antimicrobials in food-producing animals, antibiotic resistance in humans, and adverse human health consequences as a result. We believe that there is a preponderance of evidence that the use of antimicrobials in food-producing animals has adverse human consequences." "There is little evidence to the contrary."

<u>2005 Codex Alimentarius Commission (Codex), "Code of Practice to Minimize and Contain Antimicrobial Resistance" (Code of Practice)</u>

The Code of Practice provides guidance for the responsible and prudent use of antimicrobials in food-producing animals *(Ref. 15)*. Its objectives are to minimize adverse impacts on public health associated with the use of antimicrobial drugs in food-producing animals.

The Code of Practice makes a number of recommendations regarding the responsible use of antimicrobials in food-producing animals. For example, the document recommends that responsible use 1) should be controlled by the veterinary profession or other parties with the requisite expertise, and 2) does not include the use for growth promotion of veterinary antimicrobial drugs that belong to or are able to cause cross-resistance to classes

of antimicrobial agents used in humans (or submitted for approval for use in humans) in the absence of an appropriate risk analysis.

2006 Antimicrobial Resistance: Implications for the Food System, Comprehensive Reviews in Food Science and Food Safety

This report was conducted under the auspices of the Institute of Food Technologists and the IFT foundation *(Ref. 16)*. The panelists found the extent to which antibiotic use in food animals produces clinically important antibiotic resistant infections in humans is unknown. However, they do state in their recommendations that "In veterinary medicine and production agriculture implementation of various management strategies (such as responsible use guidelines, quality assurance programs, and antibiotic alternatives), coupled with government regulations, should decrease opportunities for the selection of antibiotic resistant microorganisms." Specifically, they stated "Always practice prudent use of antimicrobials to limit resistance selection and to maintain maximal benefit of antimicrobials in the future."

2009 American Academy of Microbiology. Antibiotic Resistance: An Ecological Perspective on an Old Problem

This report emphasizes the ecological fact that antibiotic resistance is a natural phenomenon that cannot be eliminated *(Ref. 17)*. The practical approach is to find effective ways to cope with antibiotic resistant bacteria harmful to humans and animals and to control the development of new types of resistance. Controlling antibiotic-resistant bacteria and subsequent infections requires vigilance on many fronts. The prudent and responsible use of antibiotics and the elimination of unnecessary use (e.g., viral infections; unnecessary, prolonged treatment) are noted as mandatory steps to an appropriate public health strategy to limit infections by resistant organisms.

2011 WHO Report: Tackling antibiotic resistance from a food safety perspective in Europe

This report follows a long series of WHO reports addressing antibiotic resistance in the food chain *(Ref. 18)*. The WHO continues to highlight the urgent need for action in remediating antibiotic resistance through a holistic, intersectoral, and multifaceted approach that includes all efforts to reduce unnecessary use of antibiotics, including those uses in food production. Specific regulatory strategies include: 1) eliminating the use of antibiotics as growth promoters in food animals; 2) requiring that antibiotics be administered to animals only when prescribed by a veterinarian; and 3) requiring the antibiotics identified as critically important in human medicine - especially fluoroquinolones and third- and fourth-generation cephalosporins - only be used in food animals when their use is justified.

Brief Summary of Recent Peer-Reviewed Scientific Literature

2008. Applied and Environmental Microbiology. Longitudinal study of antimicrobial resistance among *Escherichia coli* isolates from integrated multisite cohorts of humans and swine. Alali et al.

This study longitudinally examined the relationship between antimicrobial resistant *E. coli* from human wastewater and swine fecal samples and several risk factors including host species, production type, vocation (e.g., slaughter plant workers), and season. Authors reported that the higher levels of *E. coli* resistance in swine isolates as compared with human isolates was likely associated with either the past or current use of injectable antimicrobial agents (e.g., ceftiofur sodium) or the use of antimicrobial agents in feed (e.g., chlortetracycline) or water. Furthermore, slaughter plant workers were shown to be at higher risk of carrying multidrug-resistant *E. coli* than non-swine workers.

2008. Applied and Environmental Microbiology. Diversity and distribution of commensal fecal *Escherichia coli* bacteria in beef cattle administered selected subtherapeutic antimicrobials in a feedlot setting. Sharma et al.

This study investigated the influence of administration of chlortetracycline alone or in combination with sulfamethazine on the development of resistance, dissemination of defined strain types, and prevalence of resistance determinants in feedlot cattle *(Ref. 20)*. Shedding of tetracycline-resistant *E. coli* was higher in animals receiving both treatments. While tetracycline resistance was detected in cattle with no prior antimicrobial exposure, shedding of tetracycline-resistant *E. coli* was higher in animals subjected to either of the two treatments.

2008. Applied and Environmental Microbiology. Effect of subtherapeutic administration of antibiotics on the prevalence of antibiotic-resistant *Escherichia coli* bacteria in feedlot cattle. Alexander et al.

This study involved the collection of 3,300 fecal samples over a 314-day period from 300 feedlot steers receiving subtherapeutic levels of antibiotics *(Ref. 21)*. Study findings indicated that administration of tetracycline in combination with sulfamethazine clearly increased the prevalence of tetracycline- and ampicillin-resistant *E. coli* in cattle and the numbers of resistant *E. coli* organisms shed.

2009. American Journal of Veterinary Research. A metagenomic approach for determining prevalence of tetracycline resistance genes in the fecal flora of conventionally raised feedlot steers and feedlot steers raised without antimicrobials. Harvey et al.

This study compared the prevalence of tetracycline-resistance genes in the fecal flora of conventionally raised feedlot steers and feedlot steers raised without antimicrobials *(Ref. 22)*. Authors observed that the percentage of fecal samples with 11 tetracycline resistance genes was significantly higher for fecal samples from conventionally raised cattle (35/61 [57%]) than for fecal samples from antimicrobial-free cattle (16/61 [26%]).

2009. Foodborne Pathogens and Disease. Association between tetracycline consumption and tetracycline resistance in *Escherichia coli* from healthy Danish slaughter pigs. Vieira et al.

The objective of this Danish study was to investigate the association between tetracycline-resistant *Escherichia coli* isolates from the intestinal tract of healthy pigs and patterns of tetracycline consumption in the herds of origin, together with other risk factors *(Ref. 23)*. The study showed that the larger the time since the last administration of tetracycline, the lower the likelihood of isolating a resistant *E. coli* .

2009. Preventive Veterinary Medicine. Associations between reported on-farm antimicrobial use practices and observed antimicrobial resistance in generic fecal *Escherichia coli* isolated from Alberta finishing swine farms. Varga et al.

This study used statistical models to evaluate the associations between various antimicrobial use practices and resistance to antimicrobials among generic fecal Escherichia coli isolated from Alberta finishing swine *(Ref. 24)*. In-feed antimicrobial use was significantly associated with an increased risk of resistance to ampicillin, chloramphenicol, streptomycin, and sulfisoxazole in *E. coli* isolates. Chlortetracycline use in grower rations was associated with ampicillin and tetracycline resistance.

2010. International Journal of Food Microbiology. Farm-to-fork characterization of *Escherichia coli* associated with feedlot cattle with a known history of antimicrobial use. Alexander et al.

This study investigated antimicrobial-resistant *Escherichia coli* isolated from cattle fed diets containing chlortetracycline plus sulfamethazine (AS700) *(Ref. 25)*. Compared to the control, in which no feed antibiotics were administered, the prevalence of ampicillin-resistant and tetracycline-resistant *E. coli* was three- and four-fold greater in feces from treated animals respectively, but was similar between treatments for animal hide samples.

2011. Environmental Health Perspectives. Lower prevalence of antibiotic-resistant Enterococci on U.S. conventional poultry farms that transitioned to organic practices. Sapkota et al.

This study compared antimicrobial resistance in enterococci recovered from conventional poultry farms using antibiotics with farms that transitioned to antibiotic-free production practices and had just received organic certification *(Ref. 26)*. Over 40% of *Enterococcus faecalis* isolates from conventional poultry houses were multidrug resistant, compared with 10% of isolates from newly organic poultry houses. In addition, 84% of *Enterococcus faecium* isolates from conventional poultry houses were multidrug resistant, compared with 17% of isolates from newly organic poultry houses.

2011. Foodborne Pathogens and Disease. Association between antimicrobial resistance in *Escherichia coli* isolates from food animals and blood stream isolates from humans in Europe: an ecological study. Vieira et al.

The authors analyzed the correlation between the prevalence of antimicrobial resistance in *E. coli* isolates from blood stream infections in humans and in *E. coli* isolates from poultry, pigs, and cattle in 11 countries between 2005 and 2008 *(Ref. 27)*. Resistance against multiple drugs in *E. coli* isolates from food animals (especially poultry and pigs) was highly correlated with resistance in isolates from humans.

2011. BMC Microbiology. Distribution and characterization of ampicillin- and tetracycline-resistant *Escherichia coli* from feedlot cattle fed subtherapeutic antimicrobials. Mirzaagha et al.

Authors characterized *E. coli* isolates recovered from cattle that either received no dietary antimicrobials or were intermittently administered subtherapeutic levels of chlortetracycline, chlortetracycline and sulfamethazine (SMX), or virginiamycin over a 9-month feeding period *(Ref. 28)*. This study showed that strains exhibited multidrug resistance to SMX and chloramphenicol (a drug not in the antibiotic regimen) more frequently when obtained from steers fed chlortetracycline plus sulfamethazine than from cattle treated with either chlortetracycline alone or with virginiamycin. Results further suggested that the administration of chlortetracycline, even in the absence of SMX, can lead to the emergence of resistance to SMX, as well as other antibiotics, including ampicillin and chloramphenicol.

2012. Proceedings of the National Academy of Sciences. In-feed antibiotic effects on the swine intestinal microbiome. Looft et al.

This study involved pigs raised in a highly controlled environment, with one group of littermates receiving a diet containing a growth-enhancing antibiotic combination product [chlortetracycline, sulfamethazine, and penicillin (known as ASP250)] and the other receiving the same diet without the antibiotics *(Ref. 29)*. Even a low, short-term (14-day) dose of in-feed antibiotics increased the prevalence and diversity of antibiotic resistance genes, including resistance to antibiotics not administered in the study, and increased the prevalence of *E. coli*.

IV. Strategies for Controlling Antimicrobial Resistance Are Needed

As summarized above in Section III, the public health concerns associated with the use of medically important antimicrobial drugs in food-producing animals have been the subject of scientific interest for the past 40 years. FDA has considered all available information and believes that the weight of scientific evidence supports the recommendations outlined in this guidance document.

To effectively respond to the public health concerns associated with antimicrobial resistance, FDA believes it is important to broadly consider how antimicrobial drugs are being used. The scientific community generally agrees that antimicrobial drug use is a key driver for the emergence of antimicrobial-resistant bacteria. It is imperative that strategies

for controlling antimicrobial resistance include a consideration of how antimicrobial drugs are being used and measures to address those uses that are injudicious in nature.

V. Current Regulatory Framework

FDA considers the issue of antimicrobial resistance as part of its human food safety review related to new animal drugs used in food-producing animals. FDA considers an antimicrobial new animal drug to be "safe" if the agency concludes that there is "reasonable certainty of no harm to human health" from the proposed use of the drug in food-producing animals. This standard applies to safety evaluations completed prior to new animal drug approvals, as well as to those completed for drugs after approval. If this safety standard is not met before approval, the drug cannot be approved. If safety issues arise after approval, the Federal Food, Drug, and Cosmetic Act (the Act) provides grounds for withdrawal of approval of new animal drug applications for safety reasons. For example, section 512(e)(1)(B) of the Act provides for withdrawal of new animal drug application approvals when new evidence, along with evidence contained in the application, shows that the drug is not shown to be safe under the approved conditions of use. Under this provision, if FDA initiates a withdrawal action, it must produce evidence to show that there is a reasonable basis from which serious questions may be inferred about the ultimate safety of the drug and any substance that may be formed in or on food as a result of use of such drug under approved conditions. Once the agency meets this initial burden, the burden then shifts to the sponsor to demonstrate the safety of the drug (Docket no. 00N-1571, at p. 5, Mar. 16, 2004).

In 2003, FDA implemented new policies for evaluating antimicrobial resistance associated with use of antimicrobial new animal drugs in food-producing animals through the issuance of Guidance for Industry (GFI) #152, "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to their Microbiological Effects on Bacteria of Human Health Concern" (http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052519.pdf). This guidance document describes a risk-based assessment process for evaluating antimicrobial resistance associated with the use of antimicrobial new animal drugs in food-producing animals. The guidance also recommends measures for mitigating such risk.

In general, FDA's GFI #152 is premised on the concept that increasing the exposure of bacterial populations to antimicrobial drugs increases the risk of generating resistance to those antimicrobial drugs. Pursuant to this principle, the administration of medically important antimicrobial drugs to entire herds or flocks of food-producing animals (e.g., for production purposes) would represent a use that poses a qualitatively higher risk to public health than the administration of such drugs to individual animals or targeted groups of animals (e.g., to prevent, control, or treat specific diseases). In addition to factors that impact the potential extent of use of the drug, the guidance also considers such factors as the properties of the drug in question including mechanism of action and mechanism of resistance, the prevalence of zoonotic foodborne bacteria in the food-producing animal species for which the drug is intended, and the importance of the drug in question as a therapy in humans. Risk mitigating

factors that are considered include such limitations as restricting use of the drug to use by or on the order of a veterinarian.

Although FDA developed GFI #152 primarily to assess antimicrobial resistance risks as part of the new animal drug approval process, the underlying concept described above is also applicable to safety evaluations conducted for previously-approved antimicrobial new animal drugs. Therefore, FDA considers this same concept when it conducts safety evaluations for currently approved antimicrobial drugs, including those approved for use in animal feed.

From a practical standpoint, however, some significant differences exist between applying the GFI #152 risk assessment approach to the pre-approval process and applying it to safety reviews of currently-approved products. On the pre-approval side, the GFI #152 assessment process, including the various risk mitigation measures described, is taken into consideration by drug sponsors upstream in the drug development process and, in effect, steers product development in a direction that is most consistent with the guidance. On the post-approval side, FDA may examine certain currently-approved products to determine whether such products appear consistent with GFI #152. However, initiating action to withdraw an approved new animal drug application (NADA), in whole or in part, based on the results of a post-approval safety review would require the agency to make the showing required under section 512(e)(1) of the Act.

Alternatively, concerns associated with approved NADAs can sometimes be addressed through more informal processes. For example, in certain cases FDA has worked collaboratively with the sponsor of an NADA to address concerns raised regarding their product and has initiated steps to permit the sponsor to voluntarily withdraw part or all of the NADA or to revise the product labeling to address the concern. This alternative pathway can in some cases be an effective and expedient mechanism for resolving issues associated with an NADA.

VI. Status of FDA's Current Activities

In general, the antimicrobial new animal drug applications that FDA is addressing as part of its efforts to evaluate the public health concerns associated with the use of medically important antimicrobial drugs in food-producing animals can be divided into two broad categories: 1) those NADAs submitted after the issuance of GFI #152 in 2003 and for which FDA is assessing the microbiological safety of the new animal drug on a pre-approval basis using the principles outlined in GFI #152; and 2) those NADAs approved before the final version of GFI#152 was issued in 2003. In regard to the first category, FDA believes the approach outlined in GFI #152 for evaluating microbiological safety as part of the drug approval process has been very effective. As noted above, that assessment process and the associated risk mitigation measures are usually taken into consideration by industry during the drug development process. Thus, products that ultimately move forward toward approval are those products that include use conditions that are consistent with the guidance and are intended to minimize the extent to which product use would contribute to resistance development.

FDA believes the approach outlined in GFI #152 is scientifically sound and is protective of the public health. FDA recognizes that the list of drugs in Appendix A is not static and should be periodically reassessed and updated as necessary. Such reassessment is necessary to take into consideration such factors as the development of new antimicrobials for human therapy, the emergence of diseases in humans, or changes in prescribing practices in the United States. FDA will update Appendix A, as necessary, through a separate process that will also be subject to public comment.

The second category of products are those antimicrobial NADAs that were approved prior to the implementation of GFI #152. Some of the products in this category include products that were approved for use in food-producing animals more than 30 years ago. Of particular concern, as discussed in section IV, are those products that are approved for use in animal feed for production or growth-enhancing purposes. Although these products are FDA-approved, their approval occurred prior to implementation of current processes for assessing safety with respect to antimicrobial resistance. Furthermore, the scientific understanding regarding antimicrobial resistance has advanced significantly over this time frame and, as discussed earlier in this document, a number of scientific reports have raised public health concerns regarding the use of medically important antimicrobials in food-producing animals.

As a result, FDA is examining available information regarding medically important antimicrobial drugs currently approved for use in food-producing animals and considering potential steps for agency action.

VII. Recommended Principles Regarding Judicious Use in Animals

The continued availability of effective antimicrobial drugs is critically important for combating infectious disease in both humans and animals. This includes the continued availability of feed and water uses of such drugs for managing disease in animal agriculture. Therefore, it is in the interest of both human and animal health that we take a more proactive approach to considering how antimicrobial drugs are being used, and take steps to assure that such uses are appropriate and necessary for maintaining the health of humans and animals. Using medically important antimicrobial drugs as judiciously as possible is key to minimizing resistance development and preserving the effectiveness of these drugs as therapies for humans and animals. Although FDA applauds the efforts to date by various veterinary and animal producer organizations to institute guidelines for the judicious use of antimicrobial drugs, the agency believes additional, voluntary steps are needed.

To further address this public and animal health concern, FDA is recommending two additional principles about the appropriate or judicious use of medically important antimicrobial drugs in food-producing animals. These principles are consistent with the recommendations of a number of recent scientific panels or committees referenced earlier in this document including the 1997, 2000, and 2011 reports of the WHO, the 2003 IOM Report, and the 2005 Codex Code of Practice.

FDA recognizes the need to collaborate with the animal health and animal producer communities on strategies for minimizing animal health impacts or industry disruption that may be associated with the implementation of changes by animal drug sponsors to voluntarily align the use conditions of affected drug products with the principles outlined below. Furthermore, FDA intends to consult with the United States Department of Agriculture (USDA) on implementation strategies, including the development of a framework for veterinary oversight and consultation requirements. FDA is committed to assuring that the public health is protected while also assuring that the health needs of animals are addressed.

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.*

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. Production uses are not directed at any specifically identified disease, but rather are expressly indicated and used for the purpose of enhancing the production of animal-derived products. In contrast, FDA considers uses that are associated with the treatment, control, or prevention[5] of specific diseases, including administration through feed or water, to be uses that are necessary for assuring the health of food-producing animals.

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. However, FDA believes that some indications for prevention use are necessary and judicious as long as such use includes professional veterinary involvement. Veterinary involvement in the decision-making process associated with the use of medically important antimicrobial drugs is an important aspect of assuring appropriate use, including judicious prevention use. When determining the appropriateness of a prevention use, veterinarians consider several important factors such as determining the medical rationale for such use, and that such use is appropriately targeted at a specific etiologic agent and appropriately timed relative to the disease. For example, if a veterinarian determines, based on the client's production practices and herd health history, that cattle being transported or otherwise stressed are more likely to develop a certain bacterial infection, preventively treating these cattle with an antimicrobial approved for prevention of that bacterial infection would be considered a judicious use. Another example would be the prevention of necrotic enteritis in broiler chickens. In this case, the prevention use of an antimicrobial is important to manage this disease in certain flocks in the face of concurrent coccidiosis, a significant parasitic disease in chickens. On the other hand, FDA would not consider the administration of a drug to apparently healthy animals in the absence of any information

[5] Disease prevention involves the administration of an antimicrobial drug to animals, none of which are exhibiting clinical signs of disease, in a situation where disease is likely to occur if the drug is not administered.

that such animals were at risk of a specific disease to be a judicious use. The decision to use a specific drug or combination drug is generally based on factors that veterinarians are uniquely qualified to consider, including the mode of antibacterial action, drug distribution in specific tissues, and the duration of effective drug levels at the site of infection.

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.*

Most of the feed-use antimicrobial drugs are currently approved for over-the-counter use in food-producing animals for purposes that include the treatment, control, and prevention of disease as well as for production purposes (i.e., for growth promotion uses such as increased rate of weight gain). In addition to instituting voluntary measures that would limit use of medically important antimicrobial drugs in food-producing animals to uses that are considered necessary to assure the animals' health, FDA also believes it is important to phase-in the voluntary practice of including veterinary oversight or consultation in the use of these drugs. As noted above, FDA believes that this practice is an important mechanism for helping to assure appropriate use. 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. FDA recognizes that the nature of veterinary involvement can vary due to numerous factors such as geographic location and animal production setting. In fact, there are limited numbers of large animal veterinarians, which can make consultation or oversight challenging in certain situations. For example, some animal disease events require immediate attention. In some cases, veterinarians may be directly diagnosing and administering therapies, while in other cases they are visiting and consulting with producers periodically to establish customized disease management protocols for that producer's herd or flock. Of key importance to FDA is the fact that, in both of these cases, the veterinarian is involved in the decision-making process regarding antimicrobial drug use. FDA recognizes that increasing veterinary involvement in the use of antimicrobial drugs has significant practical implications for animal producers, veterinary practitioners, and the veterinary profession as whole. Therefore, FDA is particularly interested in receiving comments on strategies for effectively promoting the voluntary adoption of such a change.

VIII. Conclusion

In order to minimize the development of antimicrobial resistance, FDA believes that it is important to ensure the judicious use of medically important antimicrobial drugs in animal agriculture. We recommend several steps to accomplish this including voluntary measures that would limit medically important antimicrobial drugs to uses in food-producing animals that are considered necessary for assuring animal health and that include veterinary oversight or consultation. Such limitations would reduce overall medically important antimicrobial drug use levels, thereby reducing antimicrobial resistance selection pressure, while still maintaining the availability of these drugs for appropriate use.

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Contains Nonbinding Recommendations

#213

Guidance for Industry

New Animal Drugs and New Animal Drug Combination Products Administered in or on Medicated Feed or Drinking Water of Food-Producing Animals: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions with GFI #209

Submit comments on this guidance at any time. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. All written comments should be identified with the Docket No. FDA-2011-D-0889.

For further information regarding this document, contact William T. Flynn, Center for Veterinary Medicine (HFV-1), Food and Drug Administration, 7519 Standish Place, Rockville, MD 20855, 240-276-9084. E-mail: william.flynn@fda.hhs.gov.

Additional copies of this guidance document may be requested from the Communications Staff (HFV-12), Center for Veterinary Medicine, Food and Drug Administration, 7519 Standish Place, Rockville, MD 20855, and may be viewed on the Internet at either http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/default.htm or http://www.regulations.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine
December 2013

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Guidance for Industry

New Animal Drugs and New Animal Drug Combination Products, Administered in or on Medicated Feed or Drinking Water of Food-Producing Animals: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions with GFI #209

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the number listed on the previous page of this guidance.

I. Introduction

This guidance is intended for sponsors of approved applications for new animal drugs and new animal drug combination products containing medically important antimicrobial new animal drugs for use in or on medicated feed or water of food-producing animals. The guidance contains information for sponsors of such new animal drugs and combination products to facilitate voluntary changes to the conditions of use for such new animal drugs and combination products consistent with FDA's recommendations included in the guidance document entitled "The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals" (Judicious Use Guidance, GFI #209). In particular, the purpose of this guidance is to provide sponsors with specific recommendations on how to supplement their approved new animal drug applications to align with FDA's GFI #209.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word "should" in FDA's guidances means that something is suggested or recommended, but not required.

II. Background

On April 11, 2012, FDA finalized a guidance document entitled "The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals" (Judicious Use Guidance, GFI #209). That final guidance represents the Agency's current thinking regarding antimicrobial drugs that are medically important in human medicine and used in food-producing animals. Specifically, the final guidance discusses FDA's concerns regarding the development of antimicrobial resistance in human and animal bacterial pathogens when medically important antimicrobial drugs are used in food-producing animals in an injudicious manner. In addition,

the Judicious Use Guidance provides two recommended principles regarding the appropriate or judicious use of medically important antimicrobial drugs:

> (1) Limit medically important antimicrobial drugs to uses in animals that are considered necessary for assuring animal health, and
> (2) Limit medically important antimicrobial drugs to uses in animals that include veterinary oversight or consultation.

As noted above, the purpose of this guidance is to provide sponsors with specific recommendations on how to voluntarily modify the use conditions of their medically important antimicrobial drug products to align with the above two principles. The voluntary process outlined in this guidance would help to phase out the use of medically important antimicrobial drugs for production purposes and phase in veterinary oversight of therapeutic uses of these drugs.

A. Therapeutic Uses that Help Assure the Health of Animals

As discussed in GFI #209, FDA believes that, in light of the risk that antimicrobial resistance poses to public health, the use of medically important antimicrobial drugs for production purposes in food-producing animals does not represent a judicious use of these drugs. Such uses are typically administered through the feed or water on a herd- or flock-wide basis and are currently approved for such uses as increasing rate of weight gain or improving feed efficiency.

Production uses are not directed at any specifically identified disease, but rather are expressly indicated and used for the purpose of enhancing the production of animal-derived products. FDA believes that production use indications such as "increased rate of weight gain" or "improved feed efficiency" are no longer appropriate for the approved conditions of use for medically important antimicrobial drugs. In contrast, FDA considers uses that are associated with the treatment, control, and prevention of specific diseases to be therapeutic uses that are necessary for assuring the health of food-producing animals.

B. Veterinary Oversight

New animal drugs and new animal drug combination products are approved with one of three types of marketing status: (1) over-the-counter (OTC), (2) veterinary prescription (Rx), or (3) veterinary feed directive (VFD). Products for which adequate directions for use can be written for use by lay persons are labeled for OTC marketing status. When adequate directions can not be written in a manner that enables a layperson to use a drug safely and for the purposes for which it is intended, the drug is restricted to use under veterinary oversight as an Rx or VFD product.

FDA believes it is important to include veterinary oversight in the use of antimicrobial new animal drugs to assure their appropriate and judicious use. Veterinarians 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. As discussed in more detail below, FDA believes that the

judicious use of medically important antimicrobial new animal drugs in the feed or water of food-producing animals needs the scientific and clinical training of a licensed veterinarian.

III. Medically Important Antimicrobial Drugs

FDA uses the concepts set out in its Guidance for Industry (GFI) #152, "*Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to their Microbiological Effects on Bacteria of Human Health Concern*," in reviewing the human food safety component of new animal drug applications for medically important antimicrobial new animal drugs for use in food-producing animals. Guidance for Industry #152 includes an appendix that ranks antimicrobial drugs into three tiers, "critically important," "highly important," or "important," in regard to their human medical importance. At this time, FDA considers all antimicrobial drugs listed in Appendix A to GFI #152 (Appendix A) to be "medically important" in the context of implementing the recommendations outlined in GFI #209 and further discussed in this guidance document (GFI #213). We believe that the policy in GFI #209 and GFI #213 applies to all three tiers of medically important antimicrobial drugs at this time because each tier (and thus all of the drugs listed in Appendix A) contains drugs that have been previously assessed through the public processes used to develop GFI#152 and determined to be important for treating bacterial infections in people.

FDA recognizes that the list of drugs in Appendix A is not static and should be periodically reassessed and updated as necessary. Such reassessment is necessary to take into consideration such factors as the development of new antimicrobials for human therapy, the emergence of diseases in humans, or changes in prescribing practices in the United States. FDA intends to update Appendix A, as necessary, through a separate process that will also be subject to public comment. However, because Appendix A identifies those antimicrobials that have been determined to be medically important to human medicine, FDA believes the existing Appendix A provides adequate clarity for purposes of moving forward with the recommendations outlined in GFI #209. Therefore, the current list of medically important antimicrobial drug classes that are the subject of this guidance includes: aminoglycosides, lincosamides, macrolides, penicillins, streptogramins, sulfonamides, and tetracyclines.

IV. Voluntary Adoption of Judicious Use Principles

As discussed in the following section, FDA intends to work with affected drug sponsors to help them to voluntarily implement the principles described above through modifications to the approved conditions of use of their new animal drug products. FDA believes a voluntary approach, conducted in a cooperative and timely manner, is the most effective approach to achieve the common goal of more judicious use of medically important antimicrobials in animal agriculture.

FDA recognizes that it is equally important that the Agency also work with the veterinary and animal producer communities, the end users of these products, to ensure that their concerns are taken into consideration as these changes are implemented. One issue of concern is the

ability of producers, particularly those with smaller operations in remote locations, to have adequate access to veterinary services. Therefore, as steps are taken to phase in the voluntary changes discussed in this document, FDA is working collaboratively with United States Department of Agriculture (USDA) to engage the veterinary community and other stakeholders to explore strategic approaches (e.g., new models, pilot programs) to address this issue.

A. Voluntarily Phasing out Production Uses

FDA is concerned about the risk that antimicrobial resistance poses to public health from the use of medically important antimicrobial drugs in food-producing animals for production purposes. As a consequence of this concern, FDA will be working with affected drug sponsors who wish to voluntarily withdraw approved production uses of their medically important antimicrobial new animal drugs and combination new animal drug products. This guidance is intended to facilitate the voluntary process by providing useful information for sponsors intending to revise their approved labeling through a supplemental new animal drug application. In addition, as discussed later in this guidance, FDA is asking affected sponsors to notify the Agency within 3 months from the date of publication of this final guidance to inform us of their intentions to make these voluntary changes.

B. Need for Veterinary Oversight of Medically Important Antimicrobial Drugs Used in the Feed or Water of Food-Producing Animals

Prior to 1993, most antimicrobial drugs were approved for over-the-counter use in food-producing animals and many of these were administered through medicated feed or drinking water. At that time, the methods used by FDA to assess the microbial food safety aspects of new animal drug applications for antimicrobials intended for use in food-producing animals were not as rigorous as those used today, in part because less scientific data about the public health ramifications of antimicrobial resistance existed at that time. In addition, FDA's recommended approach for conducting pre-approval microbial food safety assessments has evolved over time as the quantity and quality of epidemiologic and other data bearing on antimicrobial resistance has improved. As a result, all antimicrobial new animal drugs for use in food-producing animals approved by CVM since 1993 have been labeled with Rx or VFD marketing status, with the exception of approvals of generic copies of existing OTC products and approvals of combination medicated feeds using existing OTC antimicrobial Type A medicated articles[1]. This shift to a marketing status requiring veterinary oversight was viewed as an important step to mitigate the microbial food safety risks of antimicrobial new animal drugs, particularly for those drugs considered to be medically important.

Based on the available scientific evidence concerning antimicrobial resistance, including information about resistance trends associated with the use of medically important antimicrobial drugs in food-producing animals, FDA believes that the judicious use of medically important antimicrobial drugs intended for use in food-producing animals should involve the scientific and

[1] A "Type A medicated article" is a concentrated new animal drug product used as a component in the manufacture of (1) another Type A medicated article, (2) an intermediate Type B medicated feed, or (3) a final formulation Type C medicated feed. See definition at 21 CFR 558.3(b)(2).

clinical training of a licensed veterinarian. This is because judicious use involves accurately identifying bacterial disease that is present or likely to be present and selecting the suitable antimicrobial drug.

In the case of prevention, judicious use includes a consideration by the veterinarian of relevant factors for determining the risk of a specific bacterial disease and for determining whether the use of medically important antimicrobials for prevention purposes is appropriate in a particular situation. The decision by the veterinarian to use a specific approved drug or combination drug is based on factors such as the mode of antibacterial action, drug distribution in specific tissues, and the duration of effective drug levels at the site of infection. Other important factors veterinarians consider when determining the appropriateness of a preventive use include whether: (1) there is evidence of effectiveness, (2) such a preventive use is consistent with accepted veterinary practice, (3) the use is linked to a specific etiologic agent, (4) the use is appropriately targeted to animals at risk of developing a specific disease, and (5) no reasonable alternatives for intervention exist. Numerous risk factors have been documented to increase susceptibility to bacterial disease, including environmental factors (such as temperature extremes and inadequate ventilation), host factors (such as age, nutrition, genetics, immune status), and other factors (such as stress of animal transport). From FDA's standpoint, the administration of a drug to animals when a veterinarian determines that there is a risk of a specific disease, based on the presence of such risk factors, could be considered judicious prevention use. For example, if a veterinarian determines, based on the client's production practices and herd health history, that cattle being transported or otherwise stressed are more likely to develop a certain bacterial infection, preventively treating these cattle with an antimicrobial approved for prevention of that bacterial infection would be considered a judicious use. Another example would be the prevention of necrotic enteritis in broiler chickens. In this case, the preventive use of an antimicrobial approved for such use is important to manage this disease in certain flocks in the face of concurrent coccidiosis, a significant parasitic disease in chickens. On the other hand, FDA would not consider the administration of a drug to apparently healthy animals in the absence of any information that such animals were at risk of a specific disease to be judicious. FDA believes that veterinarians are uniquely qualified to determine which specific disease-causing microorganisms are likely to be present in a particular situation and to determine appropriately timed administration to prevent disease based on specific, known risk.

For these reasons, in FDA's 1999 proposed rule on veterinary feed directives (64 FR 35966; July 2, 1999), the Agency gave antimicrobial resistance as a key example of a reason it can be important for medicated feed to be administered under a veterinarian's supervision. FDA stated, "control of the usage of certain antimicrobials is critical to reducing unnecessary use of such drugs in animals and to slowing or preventing the development of bacterial resistance to antimicrobial drugs."

Accordingly, FDA recommends that affected drug sponsors voluntarily revise the conditions of use of their medically important antimicrobial new animal drugs and combination new animal drug products to reflect the need for the professional oversight of a licensed veterinarian. This would mean a change from OTC to VFD status for medicated feed products and from OTC to Rx status for medicated drinking water products. A proposed timeline for making such changes is discussed in more detail below. FDA acknowledges that in order to facilitate the OTC to VFD change in marketing status, existing requirements related to the

distribution and use of VFD drugs must be updated and streamlined. Therefore, concurrent with the development of this guidance, FDA is actively pursuing revisions to the VFD regulations (in 21 CFR part 558) through the rulemaking process. Some of the key changes being considered include better alignment between the criteria for appropriate veterinary supervision or oversight and those established as part of veterinary licensing and practice requirements and streamlining administrative procedures. To facilitate the transition from OTC to VFD status, FDA believes it is critically important that changes such as these be implemented to minimize impacts on veterinarians, the animal feed industry, and animal producers.

While FDA believes that all medically important antimicrobial new animal drug products should be marketed with the appropriate professional oversight restriction, at this time FDA is most concerned with medically important antimicrobial new animal drugs and combination new animal drug products intended for use in or on the feed or water of food-producing animals. As discussed in GFI#209, FDA's current methodology for assessing antimicrobial risks associated with the use of antimicrobial new animal drugs in food-producing animals is premised on the concept that increasing the exposure of bacterial populations to antimicrobial drugs increases the risk of generating resistance to those antimicrobial drugs. Because feed or water use antimicrobial drugs are typically administered to entire herds or flocks of food-producing animals, such uses pose higher risk to public health than the administration of such drugs to individual animals or targeted groups of animals. For that reason, this guidance is focused on those medically important antimicrobial new animal drugs that are approved for use in the feed or water of food-producing animals.

C. Additional Considerations.

It is important to note that any extralabel use of medicated feed is not permitted by law (see sections 512(a)(2) and (a)(4)(A) of the FD&C Act). Neither veterinarians nor their clients may use, or direct the use of, a medicated feed in an extralabel manner. Therefore, when production claims for medically important antimicrobials are voluntarily removed from the approved labeling of these drugs, consistent with the judicious use principles of GFI #209, any further use of a drug without a production claim in medicated feed for production purposes will be considered an extralabel use and, thus, illegal.

V. Timeline for Voluntarily Implementing Changes

The Agency recognizes the significance of the proposed changes and the potential impacts such changes will have on the animal pharmaceutical industry, animal producers, the animal feed industry, and the veterinary profession. For this reason, FDA is currently pursuing a strategy for the voluntary adoption of these changes in an effort to minimize the impacts and provide for an orderly transition. FDA encourages all sponsors of affected new animal drugs and new animal drug combination products to contact the Agency and initiate steps to change product labeling and approved conditions of use through the process outlined in this guidance.

FDA also believes it is critical to see meaningful progress toward eliminating production uses of medically important antimicrobial drugs and bringing the remaining therapeutic uses of such drugs in or on the feed or water of food-producing animals under the oversight of

veterinarians. In order to ensure progress under the cooperative framework outlined in this guidance, FDA will monitor progress to assess whether these changes are being adopted along the timelines discussed below. FDA is confident that the objective of phasing in these changes can be met through the cooperative process discussed in this guidance, which is why we are initially pursuing this voluntary approach. If, after the period of evaluation of the three year phase in, we determine that adequate progress has not been made, we will consider whether further action under the existing provisions of the FD&C Act may be appropriate. To assist FDA in effectively monitoring rates of adoption in the industry, we request that sponsors of affected products (i.e., those products containing antimicrobial new animal drugs of importance to human medicine that are administered in medicated feed or drinking water of food-producing animals) notify the Agency of their intentions to engage in the voluntary process to modify their product labeling within 3 months from the date of publication of this final guidance. FDA anticipates that sponsors of affected products should be able to complete implementation of the changes discussed in this final guidance within 3 years of the date of publication.

FDA intends to keep the public apprised of progress. First, FDA is making public on its website a listing of all antimicrobial products affected by the guidance. Second, FDA intends to notify affected drug sponsors and, following the 3-month notification period, FDA intends to publish summary information to provide an indicator of the level of engagement of affected drug sponsors in the voluntary process. In addition, the public will be notified of completed changes to affected products through publication of approval of supplemental new animal drug applications.

Upon issuance of this final guidance, the Agency will monitor the progress of its strategy for the voluntary adoption of the changes outlined, including the progress of measures intended to facilitate an orderly and minimally disruptive transition. Three years from the date of publication of this final guidance, FDA intends to evaluate the rate of adoption of the proposed changes across affected products. The Agency will then consider further action as warranted in accordance with existing provisions of the FD&C Act for addressing matters related to the safety of approved new animal drugs.

FDA recognizes that the proposed changes in the use of these antimicrobial drugs have significant practical implications for animal producers, veterinary practitioners, animal drug sponsors, and feed mills. In particular, as mentioned previously, implementing changes to streamline existing VFD requirements is pivotal to facilitating the transition to greater veterinary oversight (i.e., from OTC to VFD marketing status) for many of these products. Therefore, the 3-year timeframe for voluntary phase-in noted above is intended to provide sufficient time for the necessary changes to the existing VFD requirements to be developed and implemented through notice and comment rulemaking. Although FDA is committed to completing this rulemaking process within the 3-year timeframe for implementing the changes discussed in this guidance, FDA is prepared to extend the timeframe, as necessary, to ensure that it coincides with the implementation of the revised VFD requirements.

The 3-year timeframe for voluntary phase-in is also intended to provide time for animal drug sponsors to make these changes in an efficient and practical manner, and for other stakeholders to prepare for the resulting changes in management/business practices. When several approved products are involved (e.g., combination drug approvals containing the same

active ingredients; same active ingredient in different dosage forms), sponsors are encouraged to coordinate implementation when practicable.

VI. Supplemental New Animal Drug Applications

A. Removing Production Uses/Changing Marketing Status

The procedures in this section (VI.A) apply to the situation where no new indications are being proposed. In the limited circumstances where a sponsor would be proposing that a new therapeutic indication be added, the procedures set forth at section VI.B below for submitting a supplemental application should be followed instead. As always, FDA encourages sponsors to consult with FDA prior to submitting supplemental applications to ensure that sponsors are targeting their submissions to answer questions that are relevant to the particular drug. The recommendations below, which, as guidance, establish no legally enforceable requirements, apply when sponsors who wish to voluntarily pursue judicious use changes are submitting supplemental new animal drug applications under 21 CFR 514.8.

1. Administrative Procedures

Sponsors who wish to voluntarily remove production use claims and change the marketing status for the remaining approved feed or water uses of affected products should indicate that their supplemental application is being submitted in accordance with GFI #213. Such supplemental applications do not need to include additional safety or effectiveness data. Sponsors of such applications would either (1) propose to change the marketing status to VFD or Rx and voluntarily withdraw the approval for all production uses or (2) for those applications without approved production uses, such sponsors would only propose a change in marketing status to VFD or Rx. No new indications would be proposed by the sponsors and in most cases the sponsors would only be required to submit revised labeling.

2. Applicable Supplemental New Animal Drug Application Technical Sections

Type A medicated articles and their associated medicated feeds should bear the VFD statement found in this Agency's regulations at 21 CFR 558.6(f) and medicated drinking water products (e.g., water soluble powders, concentrated solutions, etc.) should bear the Rx statement found in section 503(f)(4) of the FD&C Act (21 U.S.C. 353(f)(4)). The Type A medicated article and representative medicated feed labeling (Blue Bird) should be included in the supplemental application to verify: 1) the VFD statement found in this Agency's regulations at 21 CFR 558.6(f) has been appropriately added to all the labeling (Type A medicated article and Blue Bird feed labeling), and 2) the indications, mixing directions, feeding directions, etc., have been revised to reflect the voluntary withdrawal of the production use(s). Labeling for medicated drinking water products should be included in the supplemental application to verify: 1) the Rx statement found in section 503(f)(4) of the FD&C Act (21 U.S.C. 353(f)(4)) has been appropriately added to the labeling, and 2) the indications, directions for use, etc., have been revised to reflect the voluntary withdrawal of the production use(s).

B. Adding New Therapeutic Indications

In some cases, it has been suggested that there could be a therapeutic benefit associated with the production use of a drug. In situations where this could be the case, concerns have been raised that removing production uses from approved conditions of use will have negative animal health impacts. In those cases, where scientific evidence demonstrates a therapeutic benefit associated with the use of the drug for treating, controlling, or preventing a particular disease, sponsors could wish to seek new therapeutic indications to fill the therapeutic needs of animals.

FDA stresses that such new indications must be based on scientific evidence that such drug is safe and effective for the intended therapeutic use. Such new therapeutic indications should be directed at specifically identified diseases and should involve dosage regimens that provide the desired therapeutic effect while minimizing overall extent of use.

1. Administrative Procedures

Sponsors who wish to seek new therapeutic indications for use of affected products should indicate that their supplemental application is being submitted in accordance with GFI #213. Because new therapeutic indications are being proposed, these supplemental applications require the inclusion of additional safety and effectiveness data. These supplemental applications would need to include specific information as follows:

2. Applicable Supplemental New Animal Drug Application Technical Sections

a. Labeling

Type A medicated articles and their associated medicated feeds should bear the VFD statement found in this Agency's regulations at 21 CFR 558.6(f) and medicated drinking water products (e.g., water soluble powders, concentrated solutions, etc.) should bear the Rx statement found in section 503(f)(4) of the FD&C Act (21 U.S.C. 353(f)(4)). The Type A medicated article and representative medicated feed labeling (Blue Bird) should be included in the supplemental application to verify: 1) the VFD statement found in this Agency's regulations at 21 CFR 558.6(f) has been appropriately added to all the labeling (Type A medicated article and Blue Bird feed labeling), and 2) the indications, mixing directions, feeding directions, etc., have been revised to reflect the voluntary withdrawal of the production use(s). Labeling for medicated drinking water products should be included in the supplemental application to verify: 1) the Rx statement found in section 503(f)(4) of the FD&C Act (21 U.S.C. 353(f)(4)) has been appropriately added to the labeling, and 2) the indications, directions for use, etc., have been revised to reflect the voluntary withdrawal of the production use(s). In both cases, the labeling would need to reflect the new therapeutic indications for use.

b. Chemistry, Manufacturing, and Controls

The recommendations in this section assume there is no change in the chemistry, manufacturing and controls (CMC) information for the Type A medicated article or medicated drinking water products, including the product formulation, raw materials, manufacturing process, controls and packaging. If there are changes to the CMC information for the Type A

medicated article or medicated drinking water product associated with the new therapeutic indication, the sponsor should provide a description of such changes in the supplemental application, along with appropriate documentation and data to support the changes. See 21 CFR 514.8(b).

Medicated Drinking Water Product

If the new indication provides for use of the medicated drinking water product at the same concentration or concentration range as currently approved, no additional chemistry, manufacturing and controls (CMC) information is required. If the medicated drinking water product will be used to prepare medicated water at a different concentration than currently approved, the sponsor should address stability of the medicated drinking water at the new concentration (Ref. 1).

Type A Medicated Article

If the new indication is for a currently approved species and provides for a medicated feed inclusion rate currently approved for that species, no additional CMC information is required.

If the new indication is for a medicated feed inclusion rate outside of the currently approved inclusion rate or range (i.e., lower than the lowest currently approved inclusion rate or higher than the highest currently approved inclusion rate for that species), the sponsor should address homogeneity, non-segregation, and stability of the drug in representative medicated feeds at the higher/lower inclusion rate (Ref. 1). In addition, the sponsor should demonstrate that the approved medicated feed assay method is valid for assay of feeds manufactured at the higher/lower inclusion rate or provide a new method that is capable of assaying the feed (Refs. 2, 3, and 4).

If the new indication is for a species not currently approved, the sponsor should address homogeneity, non-segregation, stability, and medicated feed assay methodology in representative medicated feeds at the highest and lowest proposed medicated feed inclusion rates.

c. Human Food Safety

Toxicology/Residue Chemistry

Toxicology information associated with the original approval was considered for currently approved antimicrobial new animal drugs, and that information was the basis of the acceptable daily intake (ADI) that drove the residue chemistry conclusions (target tissue, tolerance, withdrawal times, etc.) for those approvals. The toxicological assessment is not expected to be reconsidered under proposed therapeutic indications with similar conditions of use to those corresponding to the production use (see Impact on Human Intestinal Flora below). If a new, proposed therapeutic indication has corresponding conditions of use (same species, with dose/duration/formulation/route of administration, etc.) that fit within existing residue chemistry parameters and are covered by previous residue chemistry evaluations, we do not anticipate that the sponsor will need to provide additional residue chemistry data or information. Sponsors are encouraged to contact CVM if they have any toxicological assessment questions.

Microbial Food Safety

Antimicrobial Resistance

It should be noted that, at the time of the original approval of older antimicrobial new animal drug applications, microbial food safety was most likely not considered in the same way or to the same extent as is currently the case. The Agency is concerned, consistent with the general elements of judicious use discussed in section II above and GFI#152, that giving antimicrobial drugs to food-producing animals at low levels for long periods of time and in large numbers of animals may contribute to antibiotic resistance. We expect any new indication(s) to (1) have an explicitly defined duration of dosing, (2) specify a therapeutic dose level, and (3) be available only to those animals that need the drug for the new indication, rather than the entire flock or herd when such use is not necessary.

Generally, these changes are expected to remove injudicious use indications, and to result only in the therapeutic use of medically important antimicrobial drugs in or on the feed or water of food-producing animals. In addition, such indications for use should include risk mitigation measures intended to reduce antimicrobial resistance when these drugs are used in or on the feed or water of food-producing animals.

To assure these goals have been met, the approval of any new indications for use would also necessitate that microbial food safety concerns be addressed consistent with the objectives of GFI #152. Prior to submission of an application, sponsors should discuss with CVM the type of information needed for this purpose. This information may include, but is not limited to:

(1) Basic information on the subject antimicrobial new animal drug, including information on mechanisms of action, spectrum of activity, resistance mechanisms, transfer of resistance, pharmacokinetics and/or pharmacodynamics if known, proposed conditions of use and how these could influence resistance development, and information on susceptibility among bacteria of human health concern;

(2) Information on the use of the subject antimicrobial new animal drug in or on the feed or water of food-producing animals, focusing on numbers of animals treated, class, consumption rates for food products from treated animals, and rates of contamination by bacteria of human health importance.

(3) Information on the use of the subject antimicrobial drug (or drugs similar to the subject drug) in human medicine. This information should address how loss of susceptibility of organisms of human health concern to the subject antimicrobial drug (or drugs similar to the subject drug) could impact human clinical medicine.

(4) Information detailing how FDA's general elements of judicious use discussed in section II have been addressed. Specifically, all approved indications should be for treatment, control and/or preventive use only, require veterinary oversight, and restrict use to an explicitly defined duration of dosing. FDA considers these measures to be significant risk mitigations consistent with the goals of GFI #152.

Upon review of this information, the Agency should be able to: 1) identify appropriate risk mitigations that would enable us to determine that the proposed use of the drug in food-producing animals is safe (i.e., a reasonable certainty of no harm to human health); and 2) advise on the types of additional information or data needed to address any existing data gaps associated with the new, proposed use of the subject antimicrobial new animal drug.

Impact of Antimicrobial Residues on Human Intestinal Flora

Based on the expected changes in use patterns for new indications described in the previous section, we do not anticipate that this issue will need to be addressed by sponsors. However, if changes in conditions of use (dose/duration/formulation/route of administration) are proposed that are expected to increase overall human exposure to residues of antimicrobial new animal drugs in animal-derived food products, then sponsors will be asked to address the safety of their proposed use with respect to impact of residues or metabolites of antimicrobial new animal drugs and compounds with antimicrobial activity on the intestinal flora of human consumers (Ref. 5).

d. Target Animal Safety

Regarding previously approved antimicrobial new animal drugs, target animal safety information associated with the original approval has already been considered. As long as any new, proposed therapeutic indication has conditions of use that are covered by previous target animal safety evaluations (same species, a dose within the approved dosage range, same or shorter duration, same route of administration, same formulation), we do not anticipate that the sponsor will need to provide additional data or information, unless the Agency becomes aware of human or animal health concerns that were not apparent at the time of the original target animal safety evaluation.

e. Evidence of Effectiveness

Sponsors seeking approval of a new therapeutic indication should provide substantial evidence in support of the effectiveness of the new animal drug for the proposed new therapeutic indication. As described in 21 CFR 514.4, the sponsor should provide information that will allow the Agency to determine that:

- parameters selected for measurement and the measured responses reliably reflect effectiveness;
- the results obtained are likely to be repeatable;
- valid inferences can be drawn from these sources to the use of the new animal drug in the target population; and
- the new animal drug is effective for the new therapeutic indication under the proposed conditions of use.

The type of information required to demonstrate effectiveness will need to be determined on a case-by-case basis and be consistent with substantial evidence as described in 21 CFR 514.4. The Center will consider data from a wide variety of sources including literature, data generated by food animal production facilities or universities, and other existing information for a substantial evidence package. Sponsors should not limit their consideration of potential useful

data to only data that is prospectively generated. Previously approved therapeutic indications that are very similar or "related" to the new therapeutic indication could also provide inferential value in support of the new indication (e.g., a new "control of bovine respiratory disease" indication added to an application that has a previously approved "treatment of bovine respiratory disease" indication with a similar dosage regimen).

Sponsors are encouraged to discuss approaches to satisfying the requirements of substantial evidence of effectiveness with CVM.

f. Environmental Impact

By regulation (see 21 CFR 514.1(b)(14)), the Environmental Impact section must include either an environmental assessment (EA) (see 21 CFR 25.40), or a claim for categorical exclusion (see 21 CFR 25.30, 25.33). Under 21 CFR 25.15(a), a claim of categorical exclusion must include a statement of compliance with the categorical exclusion criteria and must state that to the sponsor's knowledge, no extraordinary circumstances exist. "Environmental Impact Considerations" and directions for preparing an EA can be found in 21 CFR Part 25.

VII. Generic Drugs and Combinations

Revising the conditions of use in applications for a pioneer single ingredient new animal drug products may have an effect on abbreviated (generic) new animal drug applications and combination new animal drug applications that reference these single ingredient products. The effects that submission and approval of a supplement for the pioneer drug may have on these generic or combination drugs are discussed in this section. FDA intends to work expeditiously with the sponsors of affected generic and combination new animal drug applications to align their products with the revised conditions of use specified in the referenced (i.e., pioneer) applications for the single ingredient new animal drug products.

A. Generic Applications

If the approved conditions of use for a new animal drug application for a medically important antimicrobial new animal drug are revised under this guidance by voluntarily withdrawing a production use, the approved labeling for any currently approved generic application(s) that references the original new animal drug application must generally be revised in a similar fashion, as is now standard practice. FDA will contact affected generic drug sponsors when these revisions become necessary. Consistent with current practice, we expect that the generic sponsor will submit a supplemental application to come into compliance with the revised labeling of the reference listed new animal drug (RLNAD) within 60 days after FDA notifies the generic sponsor that the approved conditions of use for the RLNAD have been revised. In such cases, if the generic labeling is not revised accordingly, the generic application holder(s) faces the possibility of suspension of the generic application under section 512(c)(2)(G) of the FD&C Act (21 U.S.C. 360b(c)(2)(G)). With regard to suspension, FDA intends to follow the procedures outlined in its regulations at 21 CFR 314.153(b) relating to human generic drug

suspensions until generic new animal drug regulations implementing section 512(c)(2)(G) of the FD&C Act (21 U.S.C. 360b(c)(2)(G) are finalized.

In addition, any future generic sponsor that wants to use such a drug as its referenced listed new animal drug cannot include the production use that was voluntarily withdrawn from the pioneer application in its generic application because under section 512(n)(1)(F) of the FD&C Act (21 U.S.C. 360b(n)(1)(F)) the generic sponsor must submit labeling that is the same as the labeling approved for the referenced listed new animal drug with a few exceptions not relevant here. Furthermore, under section 512(c)(2)(A)(vii) of the FD&C Act (21 U.S.C. 360(c)(2)(A)(vii)), the Agency cannot approve an abbreviated new animal drug application unless the labeling proposed for the generic product is the same as the labeling approved for the referenced listed new animal drug with a few exceptions not relevant for purposes of this draft guidance.

B. Combination New Animal Drugs

The term *Combination new animal drug* is defined in the substantial evidence provisions of 21 CFR Part 514 to mean a new animal drug that contains more than one active ingredient or an animal drug that is applied or administered simultaneously in a single dosage form or simultaneously in or on animal feed or drinking water (See 21 CFR 514.4(c)(1)(i)). Although the term combination new animal drug applies both to products intended for use in or on animal feed and products intended for use in the drinking water of animals, the majority of approved combination new animal drug products are feed use combination drug products.

Most feed use combination new animal drugs are combinations of individual Type A medicated articles that have previously been separately approved. So, for example, a 3-way feed use combination actually involves four approved new animal drug applications, one for the combination and one for each of the three individual Type A medicated articles. The holder of an approved feed use combination new animal drug application is typically also the holder of an approved application for at least one of the individual Type A medicated articles in the combination.

1. Production Uses.

As discussed above, FDA is requesting affected sponsors to voluntarily withdraw production uses of their medically important antimicrobial new animal drugs and combination new animal drug products. In those instances where an approved combination new animal drug product with a production claim includes a medically important antimicrobial new animal drug and the sponsor of the individually approved new animal drug application for a medically important antimicrobial new animal drug has voluntarily withdrawn the production use claims, FDA expects the sponsor of the affected combination new animal drug product will voluntarily follow suit and similarly withdraw the production use claim from the combination new animal drug application. If sponsors of these affected combination new animal drug products do not voluntarily withdraw the production use claim from the combination new animal drug application, FDA intends to consider further action as warranted in accordance with existing provisions of the FD&C Act for addressing matters related to the safety of approved combination new animal drugs.

2. Remaining Therapeutic Uses.

As discussed at section IV above, based on a number of factors FDA believes that the judicious use of medically important antimicrobial drugs intended for use in food-producing animals needs the scientific and clinical training of a licensed veterinarian. This belief applies not only to individual medically important antimicrobial new animal drugs but also to combination new animal drug products incorporating such drugs. However, as previously discussed, in recognition of the significant practical implications of revising the marketing status for these products, FDA has expressed its intent to pursue a strategy for voluntarily phasing in these changes over time in an effort to minimize the impacts and provide for an orderly transition. As explained more fully in section V, FDA is proposing clear timelines for sponsors of the affected products to make these changes in order to ensure effective progress under the cooperative framework outlined in this guidance.

However, once a sponsor of an individual Type A medicated article that is also part of a combination new animal drug submits a supplement to switch the marketing status of the individual product to VFD or Rx, FDA expects the sponsor of the affected combination new animal drug product to voluntarily follow suit. Indeed, for a combination new animal drug product containing individual Type A medicated articles intended for use in or on animal feed, this outcome is essentially compelled since a voluntary switch to VFD marketing status by one or more of the sponsors of the individual Type A medicated articles will automatically trigger the requirement for a VFD to be issued before the affected combination new animal drug product can be used in or on animal feed. This is the case because under section 504(a)(1) of the FD&C Act, "[a]ny animal feed bearing or containing a veterinary feed directive drug shall be fed to animals only by or upon a lawful veterinary feed directive issued by a licensed veterinarian in the course of the veterinarian's professional practice." (21 USC 354(a)(1)). Thus, the requirement for a VFD to be issued applies whenever a VFD drug will be used in feed, regardless of whether the VFD drug is being used by itself or in combination with other drugs. Because a voluntary switch to VFD marketing status by one or more of the Type A medicated articles contained in a combination new animal drug product results, by operation of law, in the requirement for a VFD to be issued before a feed containing the combination new animal drug product can be fed to animals, in effect, the combination new animal drug product takes on VFD status also.

Therefore, we believe that in such instances the combination new animal drug product sponsors should also submit their own supplements to formally change the marketing status of the affected combination new animal drug products to VFD in a timely manner.

This outcome is consistent with the Agency's policy, as expressed in the substantial evidence notice of proposed rulemaking (62 FR 59835; Nov. 5, 1997) which provides that a combination new animal drug should generally bear VFD or Rx marketing status if one or more of the new animal drugs that make up the combination product were individually approved with VFD or Rx marketing status for any of the intended uses or conditions of use that are also applicable to the combination product.

VIII. References

1. FDA 2008. Guidance for Industry 5: Drug Stability Guidelines
2. FDA 2005. Guidance for Industry 135: Validation of Analytical Procedures for Type C Medicated Feeds
3. FDA 2007. Guidance for Industry #136: Protocols for the Conduct of Method Transfer Studies for Type C Medicated Feed Assay Methods
4. FDA 2007. Guidance for Industry #137: Analytical Methods Description for Type C Medicated Feeds
5. FDA 2013. Guidance for Industry #159: Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Establish a Microbiological ADI VICH GL36(R)
6. FDA 2012. Guidance for Industry #209: The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals

Available at:
https://www.avma.org/KB/Resources/Pages/VFD123.aspx

Veterinary Feed Directive (VFD) Basics

VFD Resources

- **STEPS to determine the need for a VFD or prescription**
- **How to complete a VFD form**
- **VFD form** (PDF)

The 123s of VFDs

Effective January 1, 2017, stricter **federal rules** will regulate how medically important antibiotics—medications that are important for treating human disease—can be administered to animals in feed and drinking water. Among the provisions, the U.S. Food and Drug Administration will require veterinary oversight whenever such antibiotics are administered to any food animal species via feed or water, ***even if the animals are not intended for food production.*** From pet rabbits and pigs, to backyard poultry, to large livestock farms, the same restrictions will apply. ***All medically important antibiotics to be used in feed or water for food animal species will require a Veterinary Feed Directive (VFD) or a prescription.***

1)Antibiotics must be used responsibly

The driving force for the initial VFD rule in 1996 and the recent revisions is improving drug availability for the benefit of

animal health and welfare, and, in turn, food safety. The increasing threat of **antibiotic resistance** (antimicrobial resistance) to both human and animal health compelled the FDA to take action by removing production uses of medically important antibiotics and implementing greater veterinary oversight by transitioning over-the-counter (OTC) antibiotics to VFD or prescription status. *Any antibiotic use can contribute to antibiotic resistance,* so it is important to avoid unnecessary or inappropriate uses of antibiotics. The use of medically important antibiotics in livestock is one factor that can contribute to increasing resistance, and the 2017 VFD revisions (published in June 2015) aim to put responsibility for their use into the hands of veterinarians, who are trained to understand not only when these medications are needed, but also what is the appropriate drug, dose, duration, and administration method to resolve infection and protect animal health and our food supply. **The expertise of the veterinarian is critical to ensuring the responsible use of antibiotics in animals.**

2)The VFD protects animals and people

The FDA and drug manufacturers have agreed to remove production uses (i.e., growth promotion, feed efficiency) for antibiotics that are medically important and to require veterinary oversight for use of these antibiotics in feed (requires a VFD) or water (requires a prescription). Under the direction of a veterinarian, the responsible and appropriate administration of antibiotics reduces the opportunity for resistance to develop, and helps preserve our supply of effective antibiotics for situations of true need to protect animal and human health. While the changes will be challenging for everyone involved, **the end result will be more responsible antibiotic use that will benefit human and animal health**.

3)Antibiotics will still be available

Veterinarians are committed to ensuring that animal health and welfare needs are met, and that needed medications be available and administered in a timely manner for treating, controlling, or preventing animal disease. Animals will still receive antibiotics when there is a clear indication of their need. Food producers will be able to work with veterinarians to ensure that animals have the care and medication they need, when they need it.

AVMA's Role in Developing the VFD Rules

What was the AVMA's role in developing the VFD rules? The AVMA has worked with regulatory agencies (FDA, USDA, CDC) and other stakeholders such as producer groups to promote responsible use of antibiotics, while ensuring that animal health needs are met and potential burdens are minimized.

We were involved from the beginning, providing input to the FDA regarding *veterinarians' needs and roles in judicious antimicrobial use*. Our volunteer leaders and staff provided the FDA with comments and suggestions for improving the VFD process. Our discussions with the FDA began by exploring how veterinarians could gain additional oversight of antimicrobials, and subsequently agreeing upon Veterinary Feed Directives as a vehicle. Although we recognized the challenges of a transition from over-the-counter (OTC) to VFD, we welcomed the opportunity to help shape the regulations.

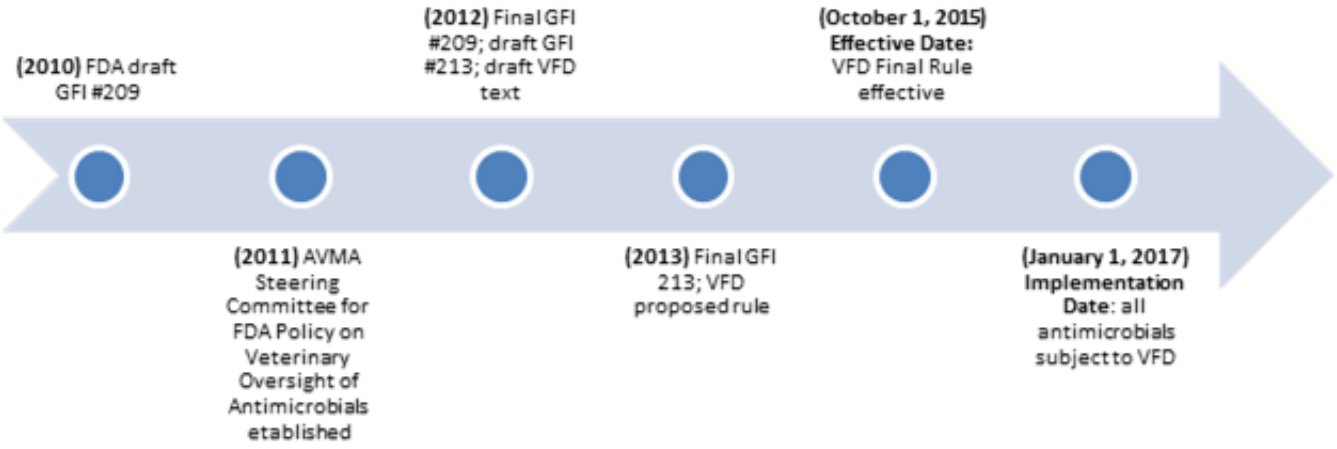
The expert AVMA members who served on the AVMA Steering Committee for FDA Policy on Veterinary Oversight of Antimicrobials provided initial thoughts on how to improve the VFD process, and the FDA incorporated many of those concepts in the 2012 draft VFD and the 2017 final rule. AVMA's interactions with the FDA were guided by two overarching policies: **The Role of the Veterinarian in Animal Antimicrobial Use** and **Veterinary Foresight and Expertise in Antimicrobial Discussions**.

AVMA's Input Influenced:

- Inclusion of a requirement that a proper **Veterinarian-Client-Patient Relationship (VCPR)** exist when a VFD is issued
- Adherence to licensing and practice requirements
- Changing the requirement from amount of feed to approximate number of animals (as feed consumption can be extremely variable and difficult to predict)

- An option for more specific identification of animals at the veterinarian's discretion (to restrict uses as needed)
- Clarification on record-keeping and formatting. For example, AVMA suggested the "written (non-verbal)" VFD and retaining VFDs electronically (as opposed to paper copies and triplicate forms)

Even with the new rule finalized, there will be remaining questions and areas of confusion. We are committed to being a resource of information and educating our members, and we **invite feedback** regarding tools or materials that would be helpful to this process.



FACT SHEET: Veterinary Feed Directive Final Rule and Next Steps

Background

Over the past several years, the FDA has taken important steps toward fundamental change in how medically important antibiotics can be legally used in feed or water for food-producing animals. Now, the agency is moving to eliminate the use of such drugs for production purposes (i.e., growth promotion and feed efficiency) and bring their remaining therapeutic uses in feed and water under the supervision of licensed veterinarians – changes that are critical to ensure these drugs are used judiciously and only when appropriate for specific animal health purposes. The Veterinary Feed Directive (VFD) final rule is an important part of the agency's overall strategy to ensure the judicious use of medically important antimicrobials in food-producing animals.

VFD Final Rule

The VFD final rule outlines the process for authorizing use of VFD drugs (animal drugs intended for use in or on animal feed that require the supervision of a licensed veterinarian) and provides veterinarians in all states with a framework for authorizing the use of medically important antimicrobials in feed when needed for specific animal health purposes.

The Veterinary Feed Directive (VFD) final rule continues to require veterinarians to issue all VFDs within the context of a veterinarian-client-patient-relationship (VCPR), and specifies the key elements that define a VCPR. These key elements include that the veterinarian engage with the client (i.e., the animal producer) to assume responsibility for making clinical judgments about patient (i.e., animal) health, have sufficient knowledge of the patient by virtue of patient examination and/or visits to the facility where the patient is managed, and provide for any necessary follow-up evaluation or care. The final rule will require veterinarians to follow state-defined VCPR requirements; in states where the FDA determines that no applicable or appropriate state VCPR requirements exist, veterinarians will need to issue VFDs in compliance with federally defined VCPR requirements. All veterinarians will need to adhere to a VCPR that includes the key elements in the final rule.

The rule facilitates veterinary oversight in a way that allows for the flexibility needed to accommodate the diversity of circumstances that veterinarians encounter, while at the same time ensuring that veterinarians in all states are conducting such oversight in accordance with nationally consistent principles. FDA will defer to individual states for the specific criteria for acceptable veterinary professional conduct when those standards require a VCPR for the issuance of a VFD and include the key elements of the federal VCPR standard. The FDA will require adherence to the federally-defined VCPR for those states with VCPR requirements that do not include the key elements of the federally-defined VCPR, or that do not require a VCPR for issuing a VFD. The agency will work with each state to review their VCPR requirements and determine if they are consistent with the federal standards.

Veterinarians play an important role in animal and human health and their oversight, as an integral part of the VFD process, will help ensure that medically important antimicrobial drugs will be used in feed according to label directions and only when appropriate to meet specific animal health needs. Currently, none of these medically important antimicrobial drugs that fall under the FDA's judicious use strategy are VFD drugs and do not require veterinary oversight or involvement. After the changes outlined in the judicious use strategy are made, medically important antimicrobials approved for use in animal feed will fall under the VFD regulation.

Next Steps: Continuing to ensure the Judicious Use of Medically Important Antimicrobials

Full implementation of FDA's Guidance #213 in December 2016 will significantly change the way medically important antibiotics have been used in animal agriculture for decades. Once the changes are fully implemented, it will be illegal to use these medically important antibiotics for production purposes, and animal producers will need to obtain authorization from a licensed veterinarian to use them for prevention, control or treatment of a specifically identified disease. All 25 affected drug sponsors have committed to implementing the changes described in Guidance #213 by the December 2016 target date.

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.

The FDA has examined the approved labels for medically important antibiotics used in feed and water and has identified that, on approximately 30 percent of the labels, there is at least one use that does not specify how long the drug should be used. However, many of these products are not currently being marketed. Once changes under Guidance #213 are fully implemented, the agency anticipates the number of products of concern will be fairly limited. The FDA is continuing to analyze this issue and examine the specific animal health conditions that are associated with open-ended or long-term duration of use. The agency is particularly interested in whether alternative approaches could better manage such conditions. This may include more targeted use of antibiotics based on labels revised to align with judicious use principles, alternative non-antibiotic therapeutic options, changes in management/production practices, or other interventions.

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 (https://www.whitehouse.gov/sites/default/files/docs/national_action_plan_for_combating_antibotic-resistant_bacteria.pdf)** 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.

Data Collection

Gathering information on the way medically important antibiotics are used is essential to measuring the impact of the FDA's judicious use strategy.

The FDA is collaborating with the U.S. Department of Agriculture and the Centers for Disease Control and Prevention to develop a plan for collecting additional data on antibiotic use to supplement existing sales data on antibiotic drugs sold for use in food-producing animals (reported under section 105 of the Animal Drug User Fee Amendments of 2008 (ADUFA 105)) and data on antibiotic resistance (collected under the **National Antimicrobial Resistance Monitoring System (/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/default.htm)**). When combined with new on-farm data, this will provide a more comprehensive and science-based picture of antibiotic drug use and resistance in animal agriculture.

This data collection plan is intended to provide the data needed to a) assess the rate of adoption of changes outlined in the FDA's Guidance #213, b) help gauge the success of stewardship efforts and guide their continued evolution and optimization, and c) assess associations between antibiotic use practices and resistance trends over time.

The FDA is continuing to work with the USDA and CDC in developing this plan and expects to hold a public meeting in the summer of 2015 in order to obtain input from the public.

Veterinary Feed Directives

Go beyond the basics to protect your practice

Know the label ***and only issue VFDs for labeled indications.***

Become **sufficiently knowledgeable** by facility visits or physical exam.

Form a VCPR ***with the client and/or caretaker.***

Check the **production facility** for husbandry, nutrition and disease issues.

Make a **presumptive diagnosis** ***that is for a labeled indication.***

Inform the client of the diagnosis, feeding instruction and your facilities findings and recommendations.

Use a template and a protocol ***to become more efficient.***

Document the medical record with the group identification, your findings, the diagnosis, your communications and client consent.

Transmit the VFD

either electronically or on paper.

Store the VFD

either in paper or electronic form.

Work by the Agricultural and Food Law Consortium is supported by the USDA National Institute of Food and Agriculture, Hatch project number 1005058, through a formal partnership with the USDA Agricultural Research Service, National Agricultural Library.

more resources are available at:

http://nationalaglawcenter.org/consortium/webinars/vfd/

Does the State or Federal VCPR Definition Apply to a Lawful VFD in my State?

21 CFR § 558.6 (b)(1) states:

(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.**

On June 11, 2015, CVM mailed a **letter (/downloads/AnimalVeterinary/DevelopmentApprovalProcess/UCM460776.pdf)** to the entity with authority over the practice of veterinary medicine in each of the 50 states and the District of Columbia. In that letter, CVM committed to publishing a list indicating whether a state-defined VCPR or a federally-defined VCPR is required for a lawful veterinary feed directive in each state. In addition CVM reported plans to post relevant correspondence received from state regulatory authorities on its Veterinary Feed Directive website. This information is presented in the table, below.

VCPR Requirement by State

State	For a lawful VFD, this VCPR definition applies:
Alabama (http://www.asbvme.alabama.gov/pdfs/2013_Alabama_Practice_Act_Administrative_Code_5_29_2013.pdf)	**Federal (http://www.ecfr.gov/cgi-bin/text-id SID=99550a83c97103df1503d4e34b99b26b&**
Alaska (https://www.commerce.alaska.gov/web/cbpl/ProfessionalLicensing/BoardofVeterinaryExaminers.aspx)	**Federal (http://www.ecfr.gov/cgi-bin/text-id SID=99550a83c97103df1503d4e34b99b26b&**
Arizona (https://vetboard.az.gov/statutes-and-rules)	State
Arkansas (http://www.arvetboard.com/sgvetboard/vetreq.asp) (http://www.fda.gov/AboutFDA/AboutThisWebsite/WebsitePolicies/Disclaimers/default.htm)	**Federal (http://www.ecfr.gov/cgi-bin/text-id SID=99550a83c97103df1503d4e34b99b26b&**
California (http://www.vmb.ca.gov/laws_regs/minstand_regs.shtml#20323)	State
Colorado (https://www.colorado.gov/dora/Veterinary)	State
Connecticut (http://www.ct.gov/dph/cwp/view.asp?a=3143&q=388948)	**Federal (http://www.ecfr.gov/cgi-bin/text-id SID=99550a83c97103df1503d4e34b99b26b&**
Delaware (http://www.dpr.delaware.gov/boards/veterinarymedicine/index.shtml)	**Federal (http://www.ecfr.gov/cgi-bin/text-id SID=99550a83c97103df1503d4e34b99b26b&**
District of Columbia (http://doh.dc.gov/node/162292)	**Federal (http://www.ecfr.gov/cgi-bin/text-id SID=99550a83c97103df1503d4e34b99b26b&**
Florida (http://www.myfloridalicense.com/Dbpr/pro/vetm/index.html) (http://www.fda.gov/AboutFDA/AboutThisWebsite/WebsitePolicies/Disclaimers/default.htm)	**Federal (http://www.ecfr.gov/cgi-bin/text-id SID=99550a83c97103df1503d4e34b99b26b&**

Georgia (http://rules.sos.ga.gov/gac/700)	**Federal (http://www.ecfr.gov/cgi-bin/text-id SID=99550a83c97103df1503d4e34b99b26b&**
Hawaii (http://cca.hawaii.gov/pvl/boards/veterinary/)	**Federal (http://www.ecfr.gov/cgi-bin/text-id SID=99550a83c97103df1503d4e34b99b26b&**
Idaho (http://adminrules.idaho.gov/rules/current/46/0101.pdf)	State
Illinois (http://www.idfpr.com/profs/vet.asp) (http://www.fda.gov/AboutFDA/AboutThisWebsite/WebsitePolicies/Disclaimers/default.htm)	State
Indiana (https://secure.in.gov/pla/2442.htm)	State
Iowa (https://www.legis.iowa.gov/law/administrativeRules/rules?agency=811&chapter=12&pubDate=08-19-2015)	State
Kansas (http://agriculture.ks.gov/divisions-programs/division-of-animal-health/kansas-board-of-veterinary-examiners/policies-and-legislature)	**Federal (http://www.ecfr.gov/cgi-bin/text-id SID=99550a83c97103df1503d4e34b99b26b&**
Kentucky (http://www.bve.ky.gov/Pages/Applications-and-Forms.aspx)	State
Louisiana (http://www.lsbvm.org/Preceptorship.htm) (http://www.fda.gov/AboutFDA/AboutThisWebsite/WebsitePolicies/Disclaimers/default.htm)	State
Maine (http://www.maine.gov/pfr/professionallicensing/professions/veterinarians/laws.html)	State
Maryland (http://mda.maryland.gov/vetboard/Pages/homepage.aspx)	**Federal (http://www.ecfr.gov/cgi-bin/text-id SID=99550a83c97103df1503d4e34b99b26b&**
Massachusetts (http://www.mass.gov/ocabr/licensee/dpl-boards/vt/)	**Federal (http://www.ecfr.gov/cgi-bin/text-id SID=99550a83c97103df1503d4e34b99b26b&**
Michigan (http://www.michigan.gov/lara/0,4601,7-154-35738_5698-118525--,00.html)	**Federal (http://www.ecfr.gov/cgi-bin/text-id SID=99550a83c97103df1503d4e34b99b26b&**
Minnesota (http://mn.gov/boards/veterinary-medicine/)	State
Mississippi (http://mississippivetboard.org/forms-2/#Veterinarians) (http://www.fda.gov/AboutFDA/AboutThisWebsite/WebsitePolicies/Disclaimers/default.htm)	State

Missouri (http://pr.mo.gov/veterinarian.asp)	State
Montana (http://bsd.dli.mt.gov/license/bsd_boards/vet_board/board_page.asp)	**Federal (http://www.ecfr.gov/cgi-bin/text-id SID=99550a83c97103df1503d4e34b99b26b&** see comment
Nebraska (http://dhhs.ne.gov/publichealth/Pages/crl_medical_vet_vet_board.aspx)	State
Nevada (https://www.leg.state.nv.us/NAC/NAC-638.html) (http://www.fda.gov/AboutFDA/AboutThisWebsite/WebsitePolicies/Disclaimers/default.htm)	State
New Hampshire (http://agriculture.nh.gov/divisions/veterinary/)	State
New Jersey (http://www.njconsumeraffairs.gov/regulations/Chapter-44-State-Board-of-Veterinary-Medical-Examiners.pdf)	**Federal (http://www.ecfr.gov/cgi-bin/text-id SID=99550a83c97103df1503d4e34b99b26b&**
New Mexico (http://www.nmbvm.org/) (http://www.fda.gov/AboutFDA/AboutThisWebsite/WebsitePolicies/Disclaimers/default.htm)	State
New York (http://www.op.nysed.gov/prof/vetmed/)	**Federal (http://www.ecfr.gov/cgi-bin/text-id SID=99550a83c97103df1503d4e34b99b26b&**
North Carolina (http://www.ncvmb.org/) (http://www.fda.gov/AboutFDA/AboutThisWebsite/WebsitePolicies/Disclaimers/default.htm)	State
North Dakota (http://www.ndbvme.org/practice-act-board-rules/) (http://www.fda.gov/AboutFDA/AboutThisWebsite/WebsitePolicies/Disclaimers/default.htm)	State
Ohio (http://ovmlb.ohio.gov/)	State
Oklahoma (http://okvetboard.com/) (http://www.fda.gov/AboutFDA/AboutThisWebsite/WebsitePolicies/Disclaimers/default.htm)	State
Oregon (http://www.oregon.gov/OVMEB/pages/index.aspx)	State
Pennsylvania (http://www.dos.pa.gov/ProfessionalLicensing/BoardsCommissions/VeterinaryMedicine/Pages/default.aspx#.Vdyi65dlkTU)	**Federal (http://www.ecfr.gov/cgi-bin/text-id SID=99550a83c97103df1503d4e34b99b26b&**
Rhode Island (http://sos.ri.gov/documents/archives/regdocs/released/pdf/DOH/7029.pdf)	**Federal (http://www.ecfr.gov/cgi-bin/text-id SID=99550a83c97103df1503d4e34b99b26b&**

South Carolina (http://www.llr.state.sc.us/POL/Veterinary/) (http://www.fda.gov/AboutFDA/AboutThisWebsite/WebsitePolicies/Disclaimers/default.htm)	State
South Dakota (http://www.socratek.com/StateLaws.aspx?id=482400&title=39-18-34.1) (http://www.fda.gov/AboutFDA/AboutThisWebsite/WebsitePolicies/Disclaimers/default.htm)	**Federal (http://www.ecfr.gov/cgi-bin/text-id SID=99550a83c97103df1503d4e34b99b26b&**
Tennessee (https://www.tn.gov/health/article/vet-natorg)	State
Texas (http://www.veterinary.texas.gov/)	State
Utah (http://www.dopl.utah.gov/licensing/veterinary.html)	State
Vermont (https://www.sec.state.vt.us/professional-regulation/profession/veterinary-medicine.aspx) (http://www.fda.gov/AboutFDA/AboutThisWebsite/WebsitePolicies/Disclaimers/default.htm)	**Federal (http://www.ecfr.gov/cgi-bin/text-id SID=99550a83c97103df1503d4e34b99b26b&**
Virginia (http://www.dhp.virginia.gov/vet/)	State
Washington (http://www.doh.wa.gov/LicensesPermitsandCertificates/ProfessionsNewReneworUpdate/Veterinarian)	**Federal (http://www.ecfr.gov/cgi-bin/text-id SID=99550a83c97103df1503d4e34b99b26b&**
West Virginia (http://wvbvm.org/) (http://www.fda.gov/AboutFDA/AboutThisWebsite/WebsitePolicies/Disclaimers/default.htm)	State
Wisconsin (http://www.dsps.wi.gov/Default.aspx?Page=d9ccddd2-1231-4789-b1b8-41a61af53d20)	**Federal (http://www.ecfr.gov/cgi-bin/text-id SID=99550a83c97103df1503d4e34b99b26b&**
Wyoming (http://plboards.state.wy.us/vetboard/index.asp) (http://www.fda.gov/AboutFDA/AboutThisWebsite/WebsitePolicies/Disclaimers/default.htm)	State

Comment: Verification of VCPR authority was not made at the time of the last update to this posting generally due to the timing of meetings of the state veterinary licensing board. The Federal VCPR definition remains the requirement.

Last Updated: November 13, 2015

APPENDIX A: BLANK VFD IN THE RECOMMENDED COMMON FORMAT

Veterinary Feed Directive

Veterinarian: _____ **Client:** _____

Address: _____ **Address:** _____

_____ (business or home) _____

Phone: _____ **Phone:** _____

Fax or email (optional): _____ **Fax or email** (optional): _____

Drug(s) Name: _____ **Drug(s) Level:** _____ **g/ton** **Duration of use:** _____

Species and Production class: _____ **Number of reorders (refills) authorized** (if permitted by the drug approval): ____

Indications for use (as approved): _____

Caution (related to this medicated feed, if any): _____

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

Approximate Number of Animals: _____

Premises: _____

Other Identification (e.g., age, weight) (optional): _____

Special Instructions (if any): _____

Affirmation of intent (for combination VFD Drugs) (check one box)*:

(*For VFD drugs for which there are no approved VFD combinations, only the first affirmation statement should be included on the VFD)

☐ 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.

☐ 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:

Drug(s)	Drug Level(s) and any Special Instructions

☐ 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.

Withdrawal Time (if any): This VFD Feed must be withdrawn ____ days prior to slaughter

VFD Date of Issuance: _____ **(Month/Day/Year)** **VFD Expiration Date:** _____ **(Month/Day/Year)** (As specified in the approval; cannot exceed 6 months after issuance)

Veterinarian's Signature: _____

All parties must retain a copy of this VFD for 2 years after the date of issuance. 21 CFR 558.6(a)(4)

APPENDIX B: EXAMPLES OF VFDS IN THE RECOMMENDED COMMON FORMAT PRE-POPULATED BY THE SPONSOR FOR SUBMISSION TO CVM

EXAMPLE 1: A PRE-POPULATED VFD FOR A VFD DRUG THAT IS NOT APPROVED, CONDITIONALLY APPROVED, OR INDEXED FOR USE WITH OTHER ANIMAL DRUG(S)

Veterinary Feed Directive
For Mydrug

Veterinarian: _____ **Client:** _____
Address: _____ **Address:** _____
_____ (business or home) _____
Phone: _____ **Phone:** _____
Fax or email (optional): _____ **Fax or email** (optional): _____

Drug(s) Name: Mydrug **Drug(s) Level:** 100 **g/ton** **Duration of use:** 14 days

Species and Production class: Swine **Number of reorders (refills) authorized** (if permitted by the drug approval): 0

Indications for use (as approved): For the treatment of Swine Disease associated with *Bacterium pathologicum*

Caution (related to this medicated feed, if any): Not for use in pregnant sows

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

Approximate Number of Animals: _____

Premises: _____

Other Identification (e.g., age, weight) (optional): _____

Special Instructions (if any): _____

Affirmation of intent (for combination VFD Drugs):

☒ 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.

Withdrawal Time (if any): This VFD Feed must be withdrawn 5 days prior to slaughter

VFD Date of Issuance: _____ **(Month/Day/Year)** **VFD Expiration Date:** _____ **(Month/Day/Year)** (As specified in the approval; cannot exceed 6 months after issuance)

Veterinarian's Signature: _____

All parties must retain a copy of this VFD for 2 years after the date of issuance. 21 CFR 558.6(a)(4)

EXAMPLE 2: A PRE-POPULATED VFD FOR A VFD DRUG THAT IS APPROVED, CONDITIONALLY APPROVED, OR INDEXED FOR USE WITH OTHER ANIMAL DRUG(S)

Veterinary Feed Directive
For Mydrug

Veterinarian: _____ **Client:** _____
Address: _____ **Address:** _____
_____ (business or home) _____
Phone: _____ **Phone:** _____
Fax or email (optional): _____ **Fax or email** (optional): _____

Drug(s) Name: Mydrug **Drug(s) Level:** 100 g/ton **Duration of use:** 14 days

Species and Production class: Swine **Number of reorders (refills) authorized** (if permitted by the drug approval): 0

Indications for use (as approved): For the treatment of Swine Disease associated with *Bacterium pathologicum*

Caution (related to this medicated feed, if any): Not for use in pregnant sows

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

Approximate Number of Animals: _____

Premises: _____

Other Identification (e.g., age, weight) (optional): _____

Special Instructions (if any): _____

Affirmation of intent (for combination VFD Drugs) (check one box)*:
(*For VFD drugs for which there are no approved VFD combinations, only the first affirmation statement should be included on the VFD)

☐ 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.

☐ 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:

Drug(s)	Drug Level(s) and any Special Instructions

☐ 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.

Withdrawal Time (if any): This VFD Feed must be withdrawn 5 days prior to slaughter

VFD Date of Issuance: _____ **(Month/Day/Year)** **VFD Expiration Date:** _____ **(Month/Day/Year)** (As specified in the approval; cannot exceed 6 months after issuance)

Veterinarian's Signature: _____

All parties must retain a copy of this VFD for 2 years after the date of issuance. 21 CFR 558.6(a)(4)

APPENDIX C: EXAMPLES OF PRE-POPULATED VFDS IN THE RECOMMENDED COMMON FORMAT THAT HAVE SUBSEQUENTLY BEEN COMPLETED BY THE ISSUING VETERINARIAN

EXAMPLE 1: A VFD DRUG THAT IS NOT APPROVED, CONDITIONALLY APPROVED, OR INDEXED FOR USE WITH OTHER ANIMAL DRUG(S)

Veterinary Feed Directive
For Mydrug

Veterinarian: John Doe, DVM or VMD
Address: 123 Anystreet, Anytown, Anystate 00000
Phone: 111-111-1111
Fax or email (optional): _____

Client: John Smith
Address: 456 Anystreet
(business or home) Anytown, Anystate 00000
Phone: 111-111-1111
Fax or email (optional): _____

Drug(s) Name: Mydrug **Drug(s) Level:** 100 g/ton **Duration of use:** 14 days

Species and Production class: Swine **Number of reorders (refills) authorized** (if permitted by the drug approval): 0

Indications for use (as approved): For the treatment of Swine Disease associated with *Bacterium pathologicum*

Caution (related to this medicated feed, if any): Not for use in pregnant sows

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

Approximate Number of Animals: 200

Premises: 777 Country Road, Anytown, Anystate 00000

Other Identification (e.g., age, weight) (optional): All animals are between 4 and 4.5 months of age

Special Instructions (if any): OK to move the swine to Barn 5 after treatment

Affirmation of intent (for combination VFD Drugs):

[X] 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.

Withdrawal Time (if any): This VFD Feed must be withdrawn 5 days prior to slaughter

VFD Date of Issuance: 05/15/17 **(Month/Day/Year)** VFD Expiration Date: 08/01/17 **(Month/Day/Year)** (As specified in the approval; cannot exceed 6 months after issuance)

Veterinarian's Signature: My signature, DVM or VMD

All parties must retain a copy of this VFD for 2 years after the date of issuance. 21 CFR 558.6(a)(4)

EXAMPLE 2: A VFD DRUG THAT IS APPROVED, CONDITIONALLY APPROVED, OR INDEXED FOR USE WITH OTHER ANIMAL DRUG(S)

Veterinary Feed Directive
For Mydrug

Veterinarian: John Doe, DVM or VMD
Address: 123 Anystreet
Anytown, Anystate 00000
Phone: 111-111-1111
Fax or email (optional):

Client: John Smith
Address: 456 Anystreet
(business or home) Anytown, Anystate 00000
Phone: 111-111-1111
Fax or email (optional):

Drug(s) Name: Mydrug **Drug(s) Level:** 100 g/ton **Duration of use:** 14 days

Species and Production class: Swine **Number of reorders (refills) authorized** (if permitted by the drug approval): 0

Indications for use (as approved): For the treatment of Swine Disease associated with *Bacterium pathologicum*

Caution (related to this medicated feed, if any): Not for use in pregnant sows

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

Approximate Number of Animals: 200

Premises: 777 Country Road, Anytown, Anystate 00000

Other Identification (e.g., age, weight) (optional): All animals are between 4 and 4.5 months of age

Special Instructions (if any): OK to move the swine to Barn 5 after treatment

Affirmation of intent (for combination VFD Drugs) (check one box)*:
(*For VFD drugs for which there are no approved VFD combinations, only the first affirmation statement should be included on the VFD)

☐ 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.

☒ 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:

Drug(s)	Drug Level(s) and any Special Instructions
CureX	100-200 g/ton; For complete information read the label for this combination

☐ 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.

Withdrawal Time (if any): This VFD Feed must be withdrawn 5 days prior to slaughter

VFD Date of Issuance: 05/15/17 (Month/Day/Year) **VFD Expiration Date:** 08/01/17 (Month/Day/Year) (As specified in the approval; cannot exceed 6 months after issuance)

Veterinarian's Signature: My signature, DVM or VMD

All parties must retain a copy of this VFD for 2 years after the date of issuance. 21 CFR 558.6(a)(4)