# SUPPORTING ANTIMICROBIAL STEWARDSHIP IN VETERINARY SETTINGS

# GOALS FOR FISCAL YEARS 2019 – 2023

# FDA CENTER FOR VETERINARY MEDICINE

September 2018

## INTRODUCTION

Antimicrobial resistance is a national and worldwide public health challenge. Antimicrobial drugs[1] have been successfully and widely used in human and veterinary medicine for more than 60 years. When used judiciously, antimicrobials can effectively fight bacterial infections. Their use and misuse, however, can promote the development of antimicrobial-resistant bacteria. When bacteria develop resistance to an antimicrobial drug, that drug may be less effective in fighting infection caused by that bacteria. It is critical that we apply a One Health approach to address this important public health concern, including implementing good antimicrobial stewardship practices in human healthcare and veterinary settings to slow the development of resistance and extend the useful life of antimicrobials. One Health is the integrative effort of multiple disciplines working locally, nationally, and globally to attain optimal health for people, animals, and the environment.[2] The focus of this plan is on actions being taken by the Food and Drug Administration's (FDA) Center for Veterinary Medicine (CVM) and other stakeholders to support antimicrobial stewardship in veterinary settings.

As part of its regulatory mission, CVM is responsible for ensuring the safety and effectiveness of animal drugs, including antimicrobials, and has taken important steps to update the approved use conditions of medically important antimicrobials (i.e., antimicrobials important for treating human disease) to support their judicious use in food-producing animals. While important progress has been made, additional work is needed to further address the challenge of antimicrobial resistance.

[1] 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. The broader term "antimicrobial," however, 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.

[2] American Veterinary Medical Association, "One Health – What is One Health?" https://www.avma.org/KB/Resources/Reference/Pages/One-Health94.aspx, accessed September 5, 2018.

Our planned effort involves a broad set of actions intended to combat antimicrobial resistance and preserve the effectiveness of antimicrobial drugs. This includes applying a risk-based approach to evaluate new and currently approved antimicrobial products for animals, collaborating with key stakeholders to support stewardship of these products by end users, and collecting data on resistance and antimicrobial use to monitor the effectiveness of our actions to slow the development of resistance.

While CVM has implemented many important steps to support stewardship of medically important antimicrobials in animals, we believe additional steps are needed. CVM plans to initiate the actions outlined in this document in phases over the next five fiscal years. This phased approach will allow us to make needed adjustments to the plan based on critical, science-based analysis, public health impact, and ongoing engagement with stakeholders.

## BACKGROUND: LIFECYCLE OF AN ANTIMICROBIAL DRUG

CVM is responsible for ensuring that animal drugs are safe and effective for their approved conditions of use. To accomplish this, CVM conducts an extensive premarket review of the safety and effectiveness data for each animal drug and continues to monitor the safety and effectiveness of each drug after it is approved for marketing. Our activities encompass the following general categories of work:

**Pre-approval Review**

- *Effectiveness*: The drug sponsor must demonstrate that the drug works when administered to animals according to the label.

- *Target Animal Safety/User Safety*: As part of the evaluation of drug safety, CVM assesses both the safety of the drug for the animals being treated as well as for the person administering the drug to the animals.

- *Environmental Safety*: Under the National Environmental Policy Act of 1969, CVM evaluates the impact of animal drugs on the environment.

- *Human Food Safety*: For drugs intended for use in food-producing animals, CVM evaluates the safety of any drug residues that may remain in the food (meat, milk, eggs, and honey) derived from treated animals. For antimicrobial drugs, this includes evaluating the impact of antimicrobial drug residues on the intestinal microflora of humans.

- *Antimicrobial Resistance Risk Assessment*: For antimicrobial drugs intended for use in food-producing animals, CVM generally uses a qualitative risk assessment to evaluate the potential for an antimicrobial drug to impact antimicrobial resistance in humans.

- *Chemistry, Manufacturing, and Controls*: CVM evaluates whether the methods used in and the facilities and controls used for manufacturing, processing, and packing the drug are adequate to assure and preserve its identity, strength, quality, and purity.

- *Label Review*: CVM evaluates the product labeling to ensure it is accurate and not misleading. The product must be properly labeled to inform the user about how to appropriately use the product, including safety considerations and storage and handling procedures.

**Post-approval Surveillance and Monitoring**

- *Adverse Event Reporting*: We review adverse event reports submitted by the drug sponsor, veterinarians, and the public. As new information becomes available, CVM reviews it to determine if any post-approval actions (e.g., updates of product labeling) are warranted to address the safety and effectiveness of the drug.

- *Drug Labeling, Promotion, and Advertising*: During the post-approval period, CVM evaluates and updates animal drug product labeling, including antimicrobial drug labeling, and may add or change label information to ensure continued safe and effective use. CVM also evaluates promotional and advertising materials used by drug sponsors to ensure the information presented to veterinarians and consumers is truthful and consistent with approved product labeling.

- *Antimicrobial Sales and Distribution Data*: For antimicrobial drugs intended for use in food-producing animals, we review annual reports submitted by drug sponsors detailing the amount of each antimicrobial drug product sold or distributed for use in food-producing animals.

- *Antimicrobial Resistance Monitoring*: For antimicrobial drugs intended for use in food-producing animals, we monitor resistance trends among key foodborne bacteria through the National Antimicrobial Resistance Monitoring System (NARMS). NARMS, a partnership between the FDA, the Centers for Disease Control and Prevention (CDC), and the U.S. Department of Agriculture (USDA), tracks antimicrobial resistance in foodborne bacteria from humans (CDC), retail meats (FDA), and food-producing animals (USDA). NARMS helps promote and protect public health by providing information about emerging bacterial resistance, how resistant infections differ from susceptible infections, and the impact of interventions designed to limit the spread of resistance.

## SUPPORTING ANTIMICROBIAL STEWARDSHIP

### What is Antimicrobial Stewardship?

CVM believes that the concept of "antimicrobial stewardship" encompasses several important principles of judicious use that are critical to slowing the rate at which bacteria develop resistance to antimicrobial drugs. In simple terms, we believe medically important antimicrobial drugs should only be used when necessary to treat, control, or prevent disease. In addition, when such use *is* necessary, these antimicrobials should be used in an optimal manner under the oversight of a licensed veterinarian.

Although work continues on multiple fronts to more fully develop stewardship plans specific to various veterinary settings, we acknowledge and support the comprehensive definition developed by the American Veterinary Medical Association (AVMA) that defines antimicrobial stewardship

AVMA has also identified the following core principles for developing antimicrobial stewardship plans in veterinary practice settings:

1. Commit to stewardship
2. Advocate for a system of care to prevent common diseases
3. Select and use antimicrobial drugs judiciously
4. Evaluate antimicrobial drug use practices
5. Educate and build expertise

for veterinarians to be "the actions veterinarians take individually and as a profession to preserve the effectiveness and availability of antimicrobial drugs through conscientious oversight and responsible medical decision making while safeguarding animal, public, and environmental health."[3]

### Collaborative approach for fostering Antimicrobial Stewardship

CVM has broad authority to regulate the safety and effectiveness of animal drugs, including the authority to require certain drugs be limited to use under the oversight of licensed veterinarians. CVM's role in overseeing activities that relate to the practice of veterinary medicine is limited, however; given that veterinarians are licensed by the states in which they practice, such oversight generally lies with state veterinary medicine licensing boards.[4]

Other important factors such as animal husbandry and biosecurity practices can have a significant bearing on disease incidence and, in turn, on the need for antimicrobial use. CVM does not generally regulate animal husbandry or farming activities; however, we believe effectively implementing antimicrobial stewardship in veterinary settings requires a collaborative effort from a broad interdisciplinary set of stakeholders.[5] These stakeholders include drug manufacturers and distributors, feed manufacturers and distributors, veterinarians, animal producers, academic organizations, food safety advocacy groups, various federal, state, and local agencies, and other key stakeholders.

We acknowledge that a wide variety of programs (e.g., quality assurance and biosecurity programs, judicious use guidelines) have already been implemented to enhance management practices on farms and support antimicrobial stewardship. A best practice, for those administering these programs, is to review and update such programs on a regular basis as new science and management practices evolve.

### Important Steps Forward

CVM has recently taken many important steps to support antimicrobial stewardship and slow the development of antimicrobial resistance in association with the use of antimicrobial drugs in animals. Recent activities include the following:[6]

- **In 2015 CVM updated the** veterinary feed directive (VFD) regulation. The VFD regulation governs how veterinarians authorize the use of VFD drugs in animal feed. The revised regulation improves the efficiency of the VFD process, a critical step to facilitate implementation of

[3] American Veterinary Medical Association, "Antimicrobial Stewardship Definition and Core Principles," 2018, https://www.avma.org/KB/Policies/Pages/Antimicrobial-Stewardship-Definition-and-Core-Principles.aspx, accessed September 5, 2018.
[4] FDA does regulate the extralabel use of animal drugs, and such extralabel use must meet the requirements of section 512(a) of the Federal Food, Drug, and Cosmetic Act and FDA regulations at 21 CFR part 530. In implementing and enforcing the extralabel provisions of federal law, we are regulating animal drugs, not regulating the practice of veterinary medicine.
[5] Although FDA does not generally regulate farming activities, we do regulate food and drugs given to food-producing animals.
[6] For a more comprehensive list of CVM's activity on antimicrobial resistance, see Appendix 1.

Guidance for industry (GFI) #213, "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."

- **In 2017 CVM completed implementation of GFI #213.** On January 3, 2017, CVM announced that it had completed implementation of GFI #213, a process begun in 2013 to transition antimicrobial drugs with importance in human medicine – medically important antimicrobials – used in the feed or drinking water of food-producing animals to veterinary oversight and eliminate the use of these products in food-producing animals for production purposes (e.g., growth promotion). As of that date, all affected drug sponsors had either voluntarily aligned their products with CVM's recommendations in GFI #213 or had voluntarily withdrawn the product's approval. As a result of these changes, medically important antimicrobials may only be used in the feed or drinking water of food-producing animals with veterinary oversight (i.e., when authorized by a prescription or, for feed drugs, by a VFD) and can no longer be used for production (e.g., growth promotion) purposes. This represents a significant change to how antimicrobials have been used for decades in food-producing animals.

Of the 292 new animal drug applications affected by GFI #213:

- 84 were completely withdrawn by the drug's sponsor.

Of the remaining 208 applications:

- 93 applications for oral dosage form products intended for use in water were converted from over-the-counter (OTC) to prescription status.
- 115 applications for products intended for use in feed were converted from OTC to VFD status.
- Production (e.g., growth promotion) indications were withdrawn from all (31) applications that included such indications for use.

## CVM'S GOALS FOR FISCAL YEARS 2019-2023

While CVM has implemented many important steps to support stewardship of medically important antimicrobials in animals, we believe additional steps are needed. This document outlines the key goals and objectives that will be our focus during fiscal years 2019 – 2023. These key activities are organized under three goals:

1. Align antimicrobial drug product use with the principles of antimicrobial stewardship
2. Foster stewardship of antimicrobials in veterinary settings
3. Enhance monitoring of antimicrobial resistance and antimicrobial drug use in animals

CVM plans to initiate the actions outlined in this document in phases over the next five fiscal years, subject to the availability of adequate resources.[7] This phased approach will allow us to make needed adjustments based on critical, science-based analysis, public health impact, and engagement with stakeholders. We have divided our approach into two phases: phase 1 will be initiated between fiscal

[7] The federal government's fiscal year covers the period from October 1 through September 30.

years 2019 – 2021, and phase 2 actions will be initiated between fiscal years 2022 – 2023. Phases are planned targets for initiating work and do not necessarily represent when the actions will be completed.

CVM will further engage stakeholders and the public as we develop and implement the strategies for addressing individual actions identified in this plan. CVM expects to establish more specific completion timelines as part of the process of developing and implementing strategies for individual action items. CVM is committed to working collaboratively with stakeholders as we continue our efforts to mitigate development of antimicrobial resistance and promote stewardship of antimicrobials.

## GOAL 1: ALIGN ANTIMICROBIAL DRUG PRODUCT USE WITH THE PRINCIPLES OF ANTIMICROBIAL STEWARDSHIP

To align all approved medically important antimicrobial drug products with the principles of antimicrobial stewardship, CVM is undertaking three important objectives under Goal #1:

### Objective 1.1: Revise, as necessary, the use conditions for approved medically important antimicrobials in food-producing animals

In GFI #213 and outreach related to the VFD final rule, CVM stated that, in addition to veterinary oversight, the judicious use of antimicrobials should be linked to a specific etiologic agent and the antimicrobial should be administered for an appropriately targeted period, i.e., have a defined duration of use. However, approximately 40% of approved medically important antimicrobial drug applications include at least one indication of use that does not have a defined duration of use. CVM has already begun to gather information on this issue and intends to develop and implement a specific strategy for ensuring that all medically important antimicrobial drugs used in food-producing animals are labeled with an appropriately targeted duration of use.

Although all feed and drinking water uses of medically important antimicrobial drugs in food-producing animals were brought under the oversight of licensed veterinarians in conjunction with the implementation of GFI #213, a limited number of other dosage forms of these drugs (e.g., injectable products) remain on the market as over-the-counter (OTC) products. Based on the 2016 Sales and Distribution Report, approximately 95% of the total quantity of medically important antimicrobials sold or distributed are products that are approved for administration through animal feed and drinking water. Therefore, the remaining 5% of medically important antimicrobials include products that are approved for routes of administration other than feed or drinking water. Some of these products remain available as OTC products. CVM plans to issue a strategy to bring the remaining medically important antimicrobial drugs under veterinary oversight. The strategy will build on the successful model used in the implementation of GFI #213, including robust dialogue with stakeholders and updates to keep the public aware of progress being made throughout the process.

| Phase 1 Actions (initiate 2019 – 2021) |
|---|
| **Action 1.1.1:** Publish a list of medically important antimicrobial drugs administered in the feed or drinking water of food-producing animals that are approved for indications that lack a defined duration of use. |
| **Action 1.1.2:** Issue a draft strategy (e.g. GFI) to ensure that all medically important antimicrobial drugs used in the feed or drinking water of food-producing animals have an appropriately targeted duration of use. |
| **Action 1.1.3:** Issue a draft strategy (e.g. GFI) to bring all dosage forms (including, injectable, intramammary, etc.) of medically important antimicrobial drugs approved for use in food-producing animals under the oversight of a licensed veterinarian. |
| **Action 1.1.4:** Issue and implement a final strategy[8] (e.g. GFI) to bring all dosage forms (including, injectable, intramammary, etc.) of medically important antimicrobial drugs approved for use in food-producing animals under the oversight of a licensed veterinarian. |
| **Action 1.1.5:** Engage with stakeholders on how antimicrobial product label information could better support antimicrobial stewardship. |
| Phase 2 Action (initiate 2022 – 2023) |
| **Action 1.1.6:** Issue a final strategy[8] (e.g. GFI) to ensure that all medically important antimicrobial drugs used in the feed or drinking water of food-producing animals have an appropriately targeted duration of use. |

### Objective 1.2: Develop and implement a strategy for promoting antimicrobial stewardship in companion animals

We will engage with our stakeholders to develop and implement a strategy to promote the judicious use of medically important antimicrobials in companion animals to help preserve the effectiveness of medically important antimicrobials for humans and companion animals. This includes a strategy to address potential development of antimicrobial resistant bacteria in companion animals. The development of antimicrobial resistant bacteria may impact the ability to effectively treat bacterial infectious disease in companion animals and increase the potential for transfer of antimicrobial resistant bacteria from companion animals to humans through direct or indirect contact.

[8] We expect to outline in the final strategy document, the time period for fully phasing-in the updates to all affected products.

| Phase 1 Actions (initiate 2019 – 2021) |
| --- |
| **Action 1.2.1:** Obtain public input (e.g., by seeking written comment and/or holding a public meeting) regarding antimicrobial use practices in companion animals and their impact on the development of resistance. |
| **Action 1.2.2:** Ensure that all dosage forms of medically important antimicrobials for use in companion animals are under the oversight of a licensed veterinarian. |
| Phase 2 Actions (initiate 2022 – 2023) |
| **Action 1.2.3:** Develop and implement a strategy for promoting antimicrobial stewardship in companion animals. |

### Objective 1.3: Enhance processes to support new product development

GFI #152, "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern," in place since 2003, outlines a process to be used as part of the animal drug approval process to assess antimicrobial resistance risks associated with new antimicrobial products intended for use in food-producing animals. As part of this risk assessment, antimicrobial drugs are ranked according to their importance to human medicine following criteria in Appendix A of GFI #152. It is necessary that this human medical importance ranking be periodically updated to ensure that it reflects current science and medical practice. Additionally, having an up-to-date GFI #152 in place is vital to ensure there is an effective process for assessing antimicrobial resistance concerns as part of the animal drug approval process. Therefore, as part of our actions under this objective, we intend to re-examine the list of medically important antimicrobial drugs in GFI #152 and update the list and ranking process as necessary.

In addition to ensuring that antimicrobial resistance risks are addressed for new antimicrobial products approved for use in animals, and that the use of antimicrobial products currently available for use in animals is optimized, it is important that efforts be made to encourage the development of alternative therapies for addressing animal health needs. While medically important antimicrobials are valuable tools for addressing animal health needs, reducing reliance on such drugs by identifying alternatives for managing animal disease can help slow the development of resistance. Such alternatives can include changes in husbandry, biosecurity, vaccination, and other factors. However, for the purposes of this document, CVM is primarily focused on alternative animal drug products that could be used in place of medically important antimicrobials.

CVM will seek opportunities to collaborate on developing strategies for facilitating such product development and is focusing on innovative approaches to look at new and novel methods for assessing alternatives to antimicrobial drugs.

| Phase 1 Actions (initiate 2019 – 2021) |
| --- |
| **Action 1.3.1:** Publish a draft of revised Appendix A of GFI #152 to update the list of medically important antimicrobials. |
| **Action 1.3.2:** Collaborate with stakeholders and international counterparts to identify ways to encourage the development of alternatives to antimicrobials, which may include new approaches to assessing alternatives to antimicrobial drugs that could spur innovation. |

## GOAL 2: FOSTER ANTIMICROBIAL STEWARDSHIP IN VETERINARY SETTINGS

As a public health regulatory agency, CVM is responsible for ensuring that animal drugs are safe and effective. It is CVM's role to ensure that antimicrobial drug products are aligned with the principles of antimicrobial stewardship (e.g., bringing medically important antimicrobials under veterinary oversight). Such steps need to be supported with both educational and compliance activities.

In addition, we are committed to working with key stakeholders, both domestically and globally, to coordinate CVM's actions with broader global efforts to foster stewardship of antimicrobials in animals. Through these actions, we seek to ensure that users of animal antimicrobial drug products have the information they need to use these drug products in accordance with applicable requirements and guidelines intended to support antimicrobial stewardship.

### Objective 2.1: Support outreach and education by providing information on antimicrobial stewardship

It is critical that all affected stakeholders (e.g., veterinarians and animal producers) are informed and have access to the information they need to effectively implement antimicrobial stewardship in veterinary settings. We will work with affected stakeholders to identify mechanisms for enhancing the availability and accessibility of relevant information. This includes, for example, enhancing access to label information for antimicrobial drug products as well as access to information from relevant guidance documents or regulations. Establishing and maintaining effective communication with affected stakeholders is a critical element to help ensure that recommendation and requirements are understood and implemented effectively.

| Phase 1 Actions (initiate 2019 – 2021) |
| --- |
| **Action 2.1.1:** CVM, in consultation with USDA, will work with veterinary, livestock, poultry, and other animal species organizations to identify ways to develop, update, and disseminate information on antimicrobial stewardship. |
| **Action 2.1.2:** Assist academic institutions and federal partners to develop veterinary curricula or other educational materials that addresses antimicrobial stewardship in animals. |
| Phase 2 Action (initiate 2022 – 2023) |
| **Action 2.1.3:** Increase access to antimicrobial drug label information for veterinarians, animal caretakers, inspectors, and others needing to access this |

| |
|---|
| information in the field. For example, access to Blue Bird labels (i.e., a representative label used for medicated feeds, including those that contain antimicrobial new animal drugs). |

### Objective 2.2: Strengthen CVM compliance program activities to support antimicrobial stewardship

Concurrent with publication of the VFD final rule in June 2015, CVM developed a VFD inspection framework to guide field personnel as they conduct inspections of impacted producers, veterinarians, and VFD medicated feed distributors (e.g., feed mills, retailers). This inspection framework was first implemented in 2016 as part of the comprehensive VFD compliance strategy, with VFD inspections being conducted by FDA's Office of Regulatory Affairs and state feed regulatory programs, and with the Feed Manufacturing Compliance Program. During inspections, field personnel examine VFD orders, requirements for the parties involved, and recordkeeping. Our focus has been on educating affected stakeholders on the new VFD requirements, but as VFD compliance activities continue, we are shifting focus from education to ensuring compliance with the VFD regulation to further ensure the safety of animal and human health.

Additionally, to support antimicrobial stewardship, it is important that CVM focus compliance activities on ensuring that medically important antimicrobial products are being appropriately marketed (i.e., that marketed products are approved, conditionally approved, or indexed) and that their use is under the oversight of licensed veterinarians.

| Phase 1 Actions (initiate 2019 – 2021) |
|---|
| **Action 2.2.1:** In conjunction with ongoing inspection activities, publish a summary assessment of the VFD pilot inspections conducted in fiscal years 2016 – 2018. |
| **Action 2.2.2:** Expand the comprehensive VFD compliance strategy to integrate a VFD component into inspections associated with the Drug Residue Inspection Program. |
| Phase 2 Action (initiate 2022 – 2023) |
| **Action 2.2.3:** Initiate steps to identify and address the inappropriate marketing of antimicrobial drugs. (e.g., illegal marketing of unapproved animal drugs containing medically important antimicrobials) |

### Objective 2.3: Support international outreach and collaboration to foster antimicrobial stewardship in veterinary settings

Our international partners – government, industry, academia, and veterinary organizations – also have an active role in the stewardship of antimicrobials used in animals. Given that antimicrobial resistance poses a worldwide public health challenge, it is critical that CVM engage international partners as policies related to antimicrobial stewardship are developed and implemented in the international arena.

| Phase 1 Actions (initiate 2019 – 2021) |
|---|
| **Action 2.3.1:** Collaborate with other federal agencies to develop U.S. Government positions and engage international partners on activities to combat antimicrobial |

| | |
|---|---|
| | resistance. This includes engaging other developed countries and organizations like the World Organisation for Animal Health (OIE), World Health Organization (WHO), Food and Agriculture Organization of the United Nations (FAO), Codex Alimentarius, and the Transatlantic Task Force on Antimicrobial Resistance. |
| | **Action 2.3.2:** Provide technical assistance to developing countries as they develop and implement programs to support antimicrobial stewardship in animals. |

## GOAL 3: ENHANCE MONITORING OF ANTIMICROBIAL RESISTANCE AND ANTIMICROBIAL DRUG USE IN ANIMALS

In order to understand the drivers of resistance in veterinary settings and assess the impact of interventions designed to limit the development of resistance, it is essential that we have access to scientifically-sound data on antimicrobial use and resistance. To support this goal, CVM is (1) developing strategies for collecting antimicrobial drug use data; (2) enhancing the collection of data on antimicrobial resistance; and (3) increasing the exchange of information among stakeholders to aid in monitoring antimicrobial drug use practices and resistance.

Through these actions, we seek to provide a more comprehensive and science-based understanding of antimicrobial drug use and resistance in veterinary settings.

### Objective 3.1: Collect and analyze data on antimicrobial drug use in animals

CVM works closely with USDA and supports ongoing data collection efforts to gather information on antimicrobial use and stewardship practices on farms through programs such as the USDA Animal and Plant Health Inspection Service's National Animal Health Monitoring System. However, a key data gap is the limited availability of data on antimicrobial use in veterinary settings.

Work is ongoing to develop and implement scientifically sound strategies for collecting additional antimicrobial use data. In the interim, to further our understanding of available antimicrobial sales data, CVM sought comment in 2017 on a proposed methodology for applying a biomass denominator to annual data on approved or conditionally approved antimicrobial drugs sold or distributed for use in food-producing animals. The goal of CVM's proposed method is to provide adjusted estimates that represent trends in antimicrobial sales and distribution relative to the animal biomass of the livestock population. This adjusted estimate is intended to provide insight into broad shifts in the amount of antimicrobials sold for use in food-producing animals and give the agency a more nuanced view of how sales increase or decrease over time in a manner that is specific to U.S. animal production. Feedback from stakeholders will help CVM identify any modifications needed before finalizing the biomass denominator.

Additionally, in 2016, CVM funded two cooperative agreements to support data collection for on-farm antimicrobial use in U.S. animal agriculture: one to collect on-farm antimicrobial use data from the poultry and swine industries, and the other to collect on-farm antimicrobial use data for dairy cattle and feedlot cattle. These pilot data collection efforts are expected to be funded for up to five years and will help provide part of the baseline information about on-farm antimicrobial use practices. We also expect these pilot projects to assist in the development of

long-term functional and efficient systems for collecting antimicrobial use data in food animal production settings.

| Phase 1 Actions (initiate 2019 – 2021) |
|---|
| **Action 3.1.1:** Complete pilot projects initiated in 2016 to characterize antimicrobial use practices in the four major food animal species (cattle, swine, chickens, and turkeys). |
| **Action 3.1.2:** Finalize an appropriate method for applying a denominator to available antimicrobial sales and distribution data. |
| Phase 2 Action (initiate 2022 – 2023) |
| **Action 3.1.3:** Develop a long-term strategy for implementing a functional and efficient systems for collecting antimicrobial use data in animals. |

### Objective 3.2: Enhance the collection and analysis of antimicrobial resistance data

Enhanced collection and analysis of antimicrobial resistance data includes expanded NARMS sampling, development of advanced approaches for resistance surveillance, targeted studies to assess the potential role of animal feeds in the ecology of antimicrobial resistance, characterization of resistance in companion animals, and studies to document the role of specific resistance genes in compromising clinical therapy. We will also continue to collaborate with USDA's National Animal Health Laboratory Network (NAHLN) laboratories to provide insight into the current state of antimicrobial resistance in bacterial pathogens from ill animals.

Together with the NARMS partner agencies (USDA and CDC), CVM conducted a public meeting entitled "2017 Scientific Meeting of the National Antimicrobial Resistance Monitoring System," to present recommendations made by a recent FDA Science Board review of NARMS. The FDA Science Board's recommendations include expanding the scope of NARMS to test farm-raised seafood products at retail, test other foodborne bacteria for resistance traits, and additional data collection capabilities intended to strengthen the scientific basis for regulatory decision making and public health interventions to address this important medical challenge.

| Phase 1 Actions (initiate 2019 – 2021) |
|---|
| **Action 3.2.1:** Expand NARMS to characterize resistance in bacteria from additional animal species and commodities where medically important antimicrobials are used. |
| **Action 3.2.2:** Expand NARMS by monitoring antimicrobial resistance in additional bacteria species. |
| **Action 3.2.3:** Improve our understanding of antimicrobial resistance using advanced genomic technologies and bioinformatics for research and surveillance. |
| **Action 3.2.4:** Build and increase domestic capacity to monitor antimicrobial resistance in animal and zoonotic pathogens to include companion animals and animal feed. |
| Phase 2 Actions (initiate 2022 – 2023) |
| **Action 3.2.5:** Establish an information technology system that links the NAHLN and the Veterinary Laboratory Investigation and Response Network laboratories that conduct antimicrobial susceptibility testing of animal pathogens to facilitate sharing, analysis, and reporting of information through a centralized data repository. |

| |
|---|
| **Action 3.2.6:** Expand NARMS retail meat sampling to improve the representativeness of surveillance data on antimicrobial resistance in foodborne bacteria. |

### Objective 3.3: Increase data sharing and reporting to aid in the monitoring of antimicrobial drug use practices and resistance

We will continue our work to increase the exchange of information among stakeholders to aid in monitoring antimicrobial drug use practices and resistance. This includes engaging key stakeholders on such information sharing and reporting strategies and ensuring that confidential information is appropriately protected.

| Phase 1 Actions (initiate 2019 – 2021) |
|---|
| **Action 3.3.1:** Publish a comprehensive report that integrates and analyzes available information about antimicrobial use and resistance in animal agriculture to assess progress of efforts to foster antimicrobial stewardship and reduce the development of antimicrobial resistance. |
| **Action 3.3.2:** Include genomic information and accelerate data sharing using interactive software tools and bioinformatics in NARMS reports. |
| **Action 3.3.3:** Continue to provide whole genome sequencing data to the Resistome Tracker, which allows users to customize visually informative displays of antibiotic resistance genes in bacteria from around the country. |
| Phase 2 Action (initiate 2022 – 2023) |
| **Action 3.3.4:** Publish a report of the information gathered through CVM-funded cooperative agreements that characterize antimicrobial use practices in the four major food animal species (cattle, swine, chickens, and turkeys). |

## CONCLUSION

Stewardship of antimicrobial drugs in human healthcare and veterinary settings is essential to slowing the emergence of resistance and extending the useful life of effective antimicrobials. CVM is committed to advancing efforts to implement good antimicrobial stewardship practices in veterinary settings as part of our mission to protect human and animal health. It is through CVM's goals to (1) align antimicrobial drug product use with the principles of antimicrobial stewardship; (2) foster antimicrobial stewardship in veterinary settings; and (3) enhance monitoring of antimicrobial resistance and use in animals, listed here, that we aim to further preserve antimicrobial drugs to ensure human and animal health.

If you have questions about this document, please contact the Center for Veterinary Medicine at AskCVM@fda.hhs.gov.

## APPENDIX 1: TIMELINE OF CVM ACTIONS TO SUPPORT STEWARDSHIP IN VETERINARY SETTINGS

Over the past 3 decades, CVM has taken a number of steps to support antimicrobial stewardship and address public health concerns associated with the use of antimicrobial drugs in animals.

Some notable steps CVM has taken include the following:

- 1993 to present: New applications for medically important antimicrobials used in food-producing animals have only been approved as VFD or prescription products. Both marketing status designations require a veterinarian to be involved in decisions about when and how to use these products in animals.

- 1996: Together with two other federal partners (USDA and CDC), CVM established the NARMS program. Since 1996, the program has undergone several enhancements. For example, NARMS revised its animal sampling structure in 2013 to obtain more representative animal data on all four target organisms under surveillance (*Salmonella*, *Campylobacter*, *Escherichia coli*, and *Enterococcus*).

- 1997: Prohibited extralabel use of fluoroquinolones and glycopeptides. Note: While other countries approved the glycopeptide, avoparcin, for use in food-producing animals, this class was never approved or marketed for such uses in the United States.

- 2003: Published GFI #152, "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern," which established a qualitative risk assessment approach for evaluating the microbial food safety of antimicrobial new animal drugs as part of the new animal drug approval process.

- 2005: Withdrew the approval of fluoroquinolones for use in poultry. Note: fluoroquinolones are still used in some other countries for poultry; see Withdrawal of Enrofloxacin for Poultry for more information.

- 2005: Incorporated into the pre-approval safety assessment of agents for food-producing animals a step-wise approach to evaluate the effect of antimicrobial residues on human intestinal flora. One of the end points of concern is the increase of antimicrobial resistant bacteria. See GFI #159, "Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Establish a Microbiological ADI".

- 2010: Published first annual summary report on antimicrobials sold or distributed for use in food-producing animals in accordance with section 105 of the Animal Drug User Fee Amendments of 2008 (ADUFA Reports).

- 2012: Published GFI #209, "The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals," which established a framework for ending production uses (e.g., increased rate of weight gain and improved feed efficiency) of medically important antimicrobials and brought the remaining therapeutic uses of such drugs in food-producing animals under veterinary oversight.

- 2012: Prohibited certain extralabel uses of cephalosporins. Note: Fourth-generation cephalosporins have never been approved for use in food-producing animals in the United States.

- 2012 – 2013: Solicited public input on data collection and reporting related to antimicrobials sold for use in food-producing animals. In response to the comments received on reporting, CVM proposed additional tables to enhance its annual summary reports of antimicrobials sold for use in food-producing animals.

- 2013: Published GFI #213, "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," in which CVM provided more detailed guidance to sponsors regarding how to align their antimicrobial drug products with GFI #209 recommendations. More specifically, the guidance defined which drug products are affected and established a three-year implementation timeline.

- 2013: Revised the animal sampling structure in NARMS to obtain more representative animal data on all four target organisms under surveillance.

- 2013: Partnered with three state public health laboratories to collect more data on resistance in bacteria from retail meats.

- 2015: Updated the VFD regulation, which governs how veterinarians authorize the use of VFD-designated animal drugs in feed. The revised regulation improves the efficiency of the VFD process, a critical step to facilitate implementation of GFI #213 to transition the marketing status of antimicrobial drug products from OTC use to VFD use under the direction of a licensed veterinarian (veterinary oversight).

- 2015: Concurrent with the publication of the final rule updating the VFD regulation in June 2015, CVM developed a VFD inspection framework to assist field personnel as they conduct inspections of the various parties involved in the VFD process (veterinarians, distributors, and animal producers). This inspection framework looks at VFD orders, requirements for the parties involved, and recordkeeping. Our intent is to phase in compliance activities related to the VFD rule over time, with the initial phases devoted heavily to educating feed mills, retailers, veterinarians, and animal producers about VFD requirements.

- 2016: Announced a funding opportunity for antimicrobial use and resistance data collection. These collection efforts are intended to provide part of the baseline information on antimicrobial use practices in the four major food-producing animal groups (cattle, swine, chickens, and turkeys), a critical element in measuring overall impact of the agency's judicious use strategy. We also expect the data collection efforts to provide important information on methodologies to help optimize long-term strategies for collecting and reporting such data.

- 2016: Approved the first alternative to an antimicrobial drug, Imrestor. Imrestor was also the first animal drug for use in food-producing animals simultaneously reviewed and approved in both the United States and Canada.

- 2016: Sought public input on establishing appropriately targeted durations of therapeutic use of medically important antimicrobial drugs in food-producing animals.

- 2016: Issued a final rule revising the annual reporting requirements for drug sponsors of antimicrobials sold or distributed for use in food-producing animals . The additional data CVM will

gather as a result of this rulemaking will improve our understanding of how antimicrobials are sold or distributed for use in the four major food-producing species and help further target efforts to ensure judicious use of medically important antimicrobials.

- 2017: Completed implementation of GFI #213. This process transitioned medically important antimicrobial drugs used in the feed or drinking water of food-producing animals from over-the-counter status to VFD or prescription status requiring veterinary oversight and eliminated production uses (e.g., growth promotion). This represents a significant change to how antimicrobials had been used for decades in food animals.

  Of the 292 new animal drug applications initially affected by GFI #213:

  - 84 were completely withdrawn

  Of the 208 remaining applications:

  - 93 applications for oral dosage form products intended for use in water were converted from over-the-counter to prescription status
  - 115 applications for products intended for use in feed were converted from over-the-counter to veterinary feed directive status
  - Production (e.g., growth promotion) indications were withdrawn from all (31) applications that included such indications for use

- 2017: Published a paper proposing the use of a biomass denominator to adjust annual data on the amount of antimicrobials sold or distributed for use in food-producing animals in the United States. This adjusted estimate will provide insight into broad shifts in the amount of antimicrobials sold for use in food-producing animals and give the agency a more nuanced view of why sales increase or decrease over time in a manner that is specific to U.S. animal production. Such analysis will also support our ongoing efforts to encourage the judicious use of antimicrobials in food-producing animals to help ensure the continued availability of safe and effective antimicrobials for animals and humans.

- 2017: Along with its NARMS partners CDC and USDA's Food Safety and Inspection Service, released the 2015 NARMS Integrated Report. The annual report highlights antimicrobial resistance patterns in bacteria isolated from humans (by CDC), raw retail meats (by FDA), and animals at slaughter (by USDA). The report also provides information derived from whole genome sequence data about resistance genes for all *Salmonella* and some *Campylobacter* isolates. The report includes NARMS Now, a set of interactive data tools that allow users to explore the dynamics of antibiotic resistance and the genes involved. While overall resistance remains low for most human infections and there have been measurable improvements in resistance levels in some important areas, NARMS is closely monitoring a few areas of concern.

- 2017: Launched Resistome Tracker, an interactive research and data visualization tool for antibiotic resistance genes.

## APPENDIX 2: CVM FISCAL YEAR 2019 – 2023 ACTIONS TO SUPPORT STEWARDSHIP IN VETERINARY SETTINGS

| **OBJECTIVES AND ACTIONS FOR GOAL 1**<br><br>*Align antimicrobial drug product use with the principles of antimicrobial stewardship* |
|---|
| Objective 1.1: Revise, as necessary, the use conditions for approved medically important antimicrobials in food-producing animals |
| Phase 1 Actions (initiate 2019 – 2021) |
| **Action 1.1.1:** Publish a list of medically important antimicrobial drugs administered in the feed or drinking water of food-producing animals that are approved for indications that lack a defined duration of use. |
| **Action 1.1.2:** Issue a draft strategy (e.g. GFI) to ensure that all medically important antimicrobial drugs used in the feed or drinking water of food-producing animals have an appropriately targeted duration of use. |
| **Action 1.1.3:** Issue a draft strategy (e.g. GFI) to bring all dosage forms (including, injectable, intramammary, etc.) of medically important antimicrobial drugs approved for use in food-producing animals under the oversight of a licensed veterinarian. |
| **Action 1.1.4:** Issue and implement a final strategy[8] (e.g. GFI) to bring all dosage forms (including, injectable, intramammary, etc.) of medically important antimicrobial drugs approved for use in food-producing animals under the oversight of a licensed veterinarian. |
| **Action 1.1.5:** Engage with stakeholders on how antimicrobial product label information could better support antimicrobial stewardship. |
| Phase 2 Action (initiate 2022 – 2023) |
| **Action 1.1.6:** Issue a final strategy[8] (e.g. GFI) to ensure that all medically important antimicrobial drugs used in the feed or drinking water of food-producing animals have an appropriately targeted duration of use. |
| Objective 1.2: Develop and implement a strategy for promoting antimicrobial stewardship in companion animals |
| Phase 1 Actions (initiate 2019 – 2021) |
| **Action 1.2.1:** Obtain public input (e.g., by seeking written comment and/or holding a public meeting) regarding antimicrobial use practices in companion animals and their impact on the development of resistance. |

[8] We expect to outline in the final strategy document, the time period for fully phasing-in the updates to all affected products.

| |
|---|
| **Action 1.2.2:** Ensure that all dosage forms of medically important antimicrobials for use in companion animals are under the oversight of a licensed veterinarian. |
| Phase 2 Actions (initiate 2022 – 2023) |
| **Action 1.2.3:** Develop and Implement a strategy for promoting antimicrobial stewardship in companion animals. |
| Objective 1.3: Enhance processes to support new product development |
| Phase 1 Actions (initiate 2019 – 2021) |
| **Action 1.3.1:** Publish a draft of revised Appendix A of Guidance for Industry #152 to update the list of medically important antimicrobials. |
| **Action 1.3.2:** Collaborate with stakeholders and international counterparts to identify ways to encourage the development of alternatives to antimicrobials, which may include new approaches to assessing alternatives to antimicrobial drugs that could spur innovation. |
| **OBJECTIVES AND ACTIONS FOR GOAL 2**<br><br>*Foster stewardship of antimicrobials in veterinary settings* |
| Objective 2.1: Support outreach and education by providing information on antimicrobial stewardship |
| Phase 1 Actions (initiate 2019 – 2021) |
| **Action 2.1.1:** CVM, in consultation with USDA, will work with veterinary, livestock, poultry, and other animal species organizations to identify ways to develop, update, and disseminate information on antimicrobial stewardship. |
| **Action 2.1.2:** Assist academic institutions and federal partners to develop veterinary curricula or other educational materials that addresses antimicrobial stewardship in animals. |
| Phase 2 Action (initiate 2022 – 2023) |
| **Action 2.1.3:** Increase access to antimicrobial drug label information for veterinarians, animal caretakers, inspectors, and others needing to access this information in the field. For example, access to Blue Bird labels (i.e., a representative label used for medicated feeds, including those that contain antimicrobial new animal drugs). |
| Objective 2.2: Strengthen CVM compliance program activities to support antimicrobial stewardship. |
| Phase 1 Action (initiate 2019 – 2021) |
| **Action 2.2.1:** In conjunction with ongoing inspection activities, publish a summary assessment of the Veterinary Feed Directive (VFD) pilot inspections conducted in fiscal years 2016 – 2018. |
| **Action 2.2.2:** Expand the comprehensive VFD compliance strategy to integrate the VFD inspection framework into inspections associated with the Drug Residue Inspection Program. |

| |
|---|
| Phase 2 Action (initiate 2022 – 2023) |
| **Action 2.2.3:** Initiate steps to identify and address the inappropriate marketing of antimicrobial drugs. (e.g., illegal marketing of unapproved animal drugs containing medically important antimicrobials) |
| Objective 2.3: Support international outreach and collaboration to foster antimicrobial stewardship in veterinary settings |
| Phase 1 Actions (initiate 2019 – 2021) |
| **Action 2.3.1:** Collaborate with other federal agencies to develop U.S. Government positions and engage international partners on activities to combat antimicrobial resistance. This includes engaging other developed countries and organizations like the World Organisation for Animal Health (OIE), World Health Organization (WHO), Food and Agriculture Organization of the United Nations (FAO), Codex Alimentarius, and the Transatlantic Task Force on Antimicrobial Resistance. |
| **Action 2.3.2:** Provide input to developing countries as they develop and implement programs to foster the judicious use of antimicrobials in animals. |
| **OBJECTIVES AND ACTIONS FOR GOAL 3**<br><br>*Enhance monitoring of antimicrobial resistance and antimicrobial drug use in animals* |
| Objective 3.1: Collect and analyze data on antimicrobial drug use in animals |
| Phase 1 Actions (initiate 2019 – 2021) |
| **Action 3.1.1:** Complete pilot projects initiated in 2016 to characterize antimicrobial use practices in the four major food animal species (cattle, swine, chickens, and turkeys). |
| **Action 3.1.2:** Finalize an appropriate method for applying a denominator to available antimicrobial sales and distribution data. |
| Phase 2 Action (initiate 2022 – 2023) |
| **Action 3.1.3:** Develop a long-term strategy for implementing a functional and efficient antimicrobial use monitoring and reporting system for veterinary settings. |
| Objective 3.2: Enhance the collection and analysis of antimicrobial resistance data |
| Phase 1 Actions (initiate 2019 – 2021) |
| **Action 3.2.1:** Expand the National Antimicrobial Resistance Monitoring System program (NARMS) to characterize resistance in bacteria from additional animal species and commodities where medically important antimicrobials are used. |
| **Action 3.2.2:** Expand NARMS by monitoring antimicrobial resistance in additional bacteria species. |

| |
|---|
| **Action 3.2.3:** Improve our understanding of antimicrobial resistance using advanced genomic technologies and bioinformatics for research and surveillance. |
| **Action 3.2.4:** Build and increase domestic capacity to monitor antimicrobial resistance in animal and zoonotic pathogens to include companion animals and animal feed. |
| Phase 2 Actions (initiate 2022 – 2023) |
| **Action 3.2.5:** Establish an information technology system that links the National Animal Health Laboratory Network and the Veterinary Laboratory Investigation and Response Network laboratories that conduct antimicrobial susceptibility testing of animal pathogens to facilitate sharing, analysis, and reporting of information through a centralized data repository. |
| **Action 3.2.6:** Expand NARMS retail meat sampling to improve the representativeness of surveillance data on antimicrobial resistance in foodborne bacteria. |
| Objective 3.3: Increase data sharing and reporting to aid in the monitoring of antimicrobial drug use practices and resistance |
| Phase 1 Actions (initiate 2019 – 2021) |
| **Action 3.3.1:** Publish a comprehensive report that integrates and analyzes available information about antimicrobial use and resistance in animal agriculture to assess progress of efforts to foster antimicrobial stewardship and reduce the development of antimicrobial resistance. |
| **Action 3.3.2:** Include genomic information, and accelerate data sharing, using interactive software tools and bioinformatics in NARMS reports. |
| **Action 3.3.3:** Continue to provide whole genome sequencing data to the Resistome Tracker which allows users to customize visually informative displays of antibiotic resistance genes in bacteria from around the country. |
| Phase 2 Action (initiate 2022 – 2023) |
| **Action 3.3.4:** Publish a report of the information gathered through CVM-funded cooperative agreements that characterize antimicrobial use practices in the four major food animal species (cattle, swine, chickens, and turkeys). |

## ACRONYMS

| | |
|---|---|
| ADUFA | Animal Drug User Fee Act |
| AVMA | American Veterinary Medical Association |
| CDC | Centers for Disease Control and Prevention |
| CVM | Center for Veterinary Medicine |
| FDA | Food and Drug Administration |
| GFI | Guidance for Industry |
| NAHLN | National Animal Health Laboratory Network |
| NARMS | National Antimicrobial Resistance Monitoring System |
| OTC | Over-the-counter |
| USDA | United States Department of Agriculture |
| VFD | Veterinary Feed Directive |