PROGRESS MADE ON CVM'S 5 -YEAR PLAN FOR SUPPORTING ANTIMICROBIAL STEWARDSHIP IN VETERINARY SETTINGS

PHASE 1

Introduction

In 2018, the Food and Drug Administration (FDA), Center for Veterinary Medicine (CVM) announced its 5-year action plan for Supporting Antimicrobial Stewardship in Veterinary Settings. Included in that action plan are 32 distinct activities that CVM is focused on during fiscal years 2019 – 2023. These items are spread across 3 goals intended to:

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

Given the number and the complexity of the activities included, CVM divided the 5-year plan into two phases. Phase 1 was initiated between fiscal 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.

Of the 32 actions from the 5-year plan, 24 were planned to begin in Phase 1; eight actions are planned to initiate in Phase 2. Strategic placement of these actions along a 5-year timeline have allowed steady and successful advancements toward achieving our 3 goals.

Phase 1 Accomplishments

During Phase 1 (2019 – 2021), there were 24 actions initiated and 21 were completed. Below is a summary of progress made during fiscal years 2019 – 2021. This includes providing drug sponsors with documents to help align antimicrobial products with stewardship principles, developing and streamlining resources needed to educate animal care takers, and providing stakeholders time to develop a data collection plan to ensure the efforts being made are having an impact.

Goal 1: Align antimicrobial drug product use with the principles of antimicrobial stewardship

Overall Goal 1 includes 11 actions from the 5-year plan. Nine of those actions were planned for Phase 1 and are included below. Of those nine actions, eight were initiated and completed during Phase 1.

Phase 1 Action	Status	Accomplishment
1.1.1: Publish a list of medically important antimicrobial drugs administered in the feed of food-producing animals that are approved for indications that lack a defined duration of use.	Complete[1]	The List of affected applications was posted online in April 2019.

[1] Items marked "Complete" included a clear deliverable in their action (e.g., publishing a specific document document).

Phase 1 Action	Status	Accomplishment
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.	Complete/ Ongoing	In January 2021, CVM published a concept paper, "Potential Approach for Defining Durations of Use for Medically Important Antimicrobial Drugs Intended for Use In or On Feed" to obtain early input on how animal drug sponsors could voluntarily make changes to the approved conditions of use for certain medically important antimicrobial drugs to establish a defined duration of use for those indications that currently lack a defined duration of use. CVM received over 30,000 comments on this concept paper. Given the magnitude of public comments received and the complex scientific and policy related issues, CVM is developing a revised approach, in the form of a draft guidance for industry (GFI) to address the durations of use issue.
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.	Complete	In September 2019, CVM issued draft Guidance for Industry (GFI) #263, "Recommendations for Sponsors of Medically Important Antimicrobial Drugs Approved for Use in Animals to Voluntarily Bring Under Veterinary Oversight All Products That Continue to be Available Over-the-Counter." This draft GFI provides the framework, including a 2-year timeline, for transitioning from over-the-counter to prescription marketing status for all approved medically important antimicrobial drugs that are not yet subject to veterinary oversight. In conjunction with issuing this draft strategy, CVM published a list of affected new animal drug applications.
1.1.4: Issue and implement a final 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.	Complete	Final GFI #263 was published in June 2021 along with a fact sheet to address frequently asked questions for farmers and ranchers.

Phase 1 Action	Status	Accomplishment
1.1.5: Engage with stakeholders on how antimicrobial product label information could better support antimicrobial stewardship.	Complete/ Ongoing[2]	This action was accounted for when CVM received feedback on the Duration of Use concept paper and during the development of GFI #263.
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.	Initiated/ Delayed	While CVM did not make progress on this item during Phase 1, in February 2022 CVM issued a Request for Information to gain information about the use of antimicrobial drugs in companion animals.
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.	Complete/ Ongoing	Final GFI #263 was published in June 2021 and includes antimicrobial drugs that are approved for use in companion animals.
1.3.1: Publish a draft of revised Appendix A of GFI #152 to update the list of medically important antimicrobials.	Complete/ Ongoing	To obtain early input, a concept paper, "Potential Approach for Ranking of Antimicrobial Drugs According to Their Importance in Human Medicine: A Risk Management Tool for Antimicrobial New Animal Drugs," and revised ranking list (frequently referred to as Appendix A) published in October 2020. Additionally, in November 2020, CVM held a public meeting with over 200 participants to discuss this potential approach. CVM received over 60 comments from the public and is incorporating possible changes into a draft revised GFI #152, "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern."

[2] Items marked "Complete/Ongoing" are for open ended actions. These actions did have items complete during Phase 1 but its possible additional progress (e.g., providing education and outreach) could occur.

Phase 1 Action	Status	Accomplishment
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.	Complete/ Ongoing	1) CVM is the lead of the Action 3.3 Group of the Transatlantic Task Force on Antimicrobial Resistance (TATFAR) (formerly Action 3.7) to discuss the particular challenges related to authorization of novel veterinary therapies presented as alternatives to antimicrobials. 2) CVM supported outreach activities on 12/18/2019, with a presentation and panel discussion at the 3rd International Symposium on Alternatives to Antibiotics. CVM provided a similar overview of the US regulatory pathway at the 2021 Phage Futures Congress on 2/26/2021. 3) CVM is in the final stages of clearing a revision of GFI #170 as it relates to barrier to innovation waivers that include as a criterion for qualification "alternatives to drug(s) of concern for human/animal health (e.g., medically important antimicrobials)."

Goal 2: Foster stewardship of antimicrobials in veterinary settings

Overall Goal 2 includes eight actions from the 5-year plan. Six of those actions were planned for initiation in Phase 1. All six actions were initiated and completed during Phase 1.

Phase 1 Action	Status	Accomplishment
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.	Complete /Ongoing	1) In April 2020, CVM funded a jointly[3] sponsored conference focused on Judicious Use and Stewardship in Dairy Cattle. 2) Additionally, in September 2021, CVM awarded an education and outreach contract to develop information on antimicrobial resistance (AMR) and highlight the importance of stewardship and veterinary involvement. Work funded by this contract will be ongoing through 2022.

[3] Washington State University and California Department of Food and Agriculture were the collaborators.

Phase 1 Action	Status	Accomplishment
2.1.2: Assist academic institutions and federal partners to develop veterinary curricula or other educational materials that addresses antimicrobial stewardship in animals.	Complete /Ongoing	In FY 2021, four veterinary colleges began stewardship projects supported by the Veterinary Laboratory Investigation and Response Network (Vet-LIRN) . This includes: 1) A Kansas State University (with collaborators from University of Missouri) project titled "Prototype reporting and veterinarian and client educational materials for cases of antimicrobial resistant bacteria of public health importance in companion animals." The aim of this project is to develop educational booklets for veterinarians and owners of companion animals diagnosed with target AMR pathogens: carbapenem-resistant Enterobacterales (CRE), carbapenem-resistant *Pseudomonas* spp., and methicillin-resistant *Staphylococcus aureus* (MRSA). 2) A Cornell University project titled: "Lab-supported antimicrobial stewardship at the Cornell University Hospital for Animals." The aim of this project is to write a formal lab-supported stewardship plan for Cornell Hospital for Animals. The project will also develop an updated hospital antibiogram using subsidized antimicrobial testing, which will aid practitioners and veterinary students in making informed antimicrobial choices. 3) A project at The Ohio State University titled: "Building sequencing capability to address nosocomial infections in primary care and referral veterinary medical facilities." The aim of this project is to establish the impact of implementing a veterinary antimicrobial stewardship program on patient risk of nosocomial infection in primary care veterinary practices and create and disseminate antimicrobial stewardship recommendations for primary care veterinary practices in Ohio. 4) A University of Pennsylvania project titled: "A Multicenter Study to Evaluate Veterinary Students' Confidence and Competence in Antimicrobial Selection." The aim of this project is to develop and evaluate a teaching tool mnemonic, termed SODAPOP, that guides antimicrobial use decision-making, and develop a resource website for using SODAPOP and responding to carbapenem-resistant Enterobacterales (CRE) in animals.

Phase 1 Action	Status	Accomplishment
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.	Complete	The Summary Assessment of Veterinary Feed Directive Compliance Activities Conducted in Fiscal Years 2016–2018 was published in August 2019. Additionally, VFD inspection numbers and classifications will be added to the FDA-TRACK: Progress on FDA's Support of Antimicrobial Stewardship in Veterinary Settings website annually. VFD data on the site currently goes through FY 2016 – 2021.
2.2.2: Expand the comprehensive VFD compliance strategy to integrate a VFD component into inspections associated with the Drug Residue Inspection Program.	Complete	In Fiscal years 2019 and 2020, workplans allowed for up to 50 and 40 VFD inspections, respectively, to be conducted in conjunction with the Drug Residue Investigation Program, when applicable. Additionally, the Comprehensive Animal Food Inspection Compliance Program posted in February 2021, further solidifying this integration.
2.3.1: Collaborate with other federal agencies to develop U.S. Government positions and engage international partners in activities to combat antimicrobial resistance. This includes engaging other developed countries and organizations like the World Organization 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	Complete /Ongoing	1) In 2019, CVM attended the One Health AMR workshop in Geneva for policy officials on the recommendations of the United Nations' Ad Hoc Interagency Coordination Group (IACG) on Antimicrobial Resistance. The discussions focused on how to expedite the implementation of the IACG recommendations and contribute to a strengthened global antimicrobial resistance response. 2) In 2019, CVM provided technical assistance to FDA's Europe Office Meeting with UK VMD to discuss new EU veterinary medicines regulations. 3) In April 2019, CVM experts drafted and coordinated agency clearance of an OIE One Health Article, published in several languages. 4) CVM plays a leading role in the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR). The current work plan addresses many aspects of resistance in human and veterinary medicine.

Phase 1 Action	Status	Accomplishment
2.3.2: Provide technical assistance to developing countries as they develop and implement programs to support antimicrobial stewardship in animals	Complete	1) FDA participates in the WHO-GFN, which recently was restarted to address worldwide food laboratory testing capacity. 2) FDA is also currently contributing to the Codex Task Force on AMR to develop a guideline on integrated surveillance of AR for member countries to utilize for establishing priorities for surveillance along the food chain. 3) CVM supports regional capacity building of AR surveillance by supporting the WHO Global Action Plan. FDA-CVM supports regional capacity building of AR surveillance by supporting the WHO Global Action Plan (GAP) and is mentoring a project in Argentina to help implement an integrated surveillance program on AMR along the food chain. FDA is also contributing to the GAP through development and implementation of global integrated surveillance for ESBL-producing *E. coli* using a 'One Health' approach. 4) FDA recently contributed to revision of the WHO List of Critically Important Antimicrobials. This list was just published and is utilized globally, especially by countries where no national lists exist to guide the risk management of antimicrobial resistance as a result of medically important antimicrobial use in food animals. 5) FDA collaborates and builds partnerships with other monitoring programs in the American region, including Canada and Mexico, through routine data sharing and communication.

Goal 3: Enhance monitoring of antimicrobial resistance and antimicrobial drug use in animals

Overall, Goal 3 includes 13 actions in the 5-year plan. Nine of those actions were planned for Phase 1. Of those Nine actions, seven actions were initiated and completed during Phase 1.

Phase 1 Action	Status	Accomplishment
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).	Initiated/ Delayed	CVM has identified the gathering of information on how antimicrobials are used in animals as a priority activity to aid understanding of the drivers of resistance in animal agriculture, as well as to assess antimicrobial stewardship activities. Since 2016, CVM has funded two cooperative agreements for collecting and reporting antimicrobial use data in the four major food-producing species. These pilot projects are also developing methodologies to inform development of long-term antimicrobial use data collection strategies. These grants were scheduled to be completed by August 2021; however, both grants experienced delays in data collection activities due to COVID-19 throughout 2020 and 2021. Both applied for and received no cost extensions in order to complete the work. These groups published a series of papers in a 2020 describing the first few years of data collection (in one issue of the journal, *Zoonoses and Public Health*). CVM anticipates the remainder of the projects to be completed in 2022. In addition, FDA also funded two ongoing cooperative agreements that are piloting antimicrobial use data collection methodologies for companion animal veterinary practices, with anticipated date of completion in 2025.

Phase 1 Action	Status	Accomplishment
3.1.2: Finalize an appropriate method for applying a denominator to available antimicrobial sales and distribution data.	Complete	CVM has finalized its method for applying a denominator to antimicrobial sales and distribution data. CVM expects to see the first application of a biomass denominator included in a comprehensive report on antimicrobial stewardship that integrates and analyzes available information about antimicrobial use and resistance in animal agriculture. It is anticipated this report will publish in 2022. Going forward, CVM will pursue publication of biomass corrected antimicrobial sales data estimates in a dashboard on its website.
3.2.1: Expand NARMS to characterize resistance in bacteria from additional animal species and commodities where medically important antimicrobials are used.	Complete /Ongoing	In April 2018 NARMS launched a veal pilot study in 8 retail meat surveillance sites. Participating sites were asked to collect 10 veal samples for 6 months. Each sample was tested for *Salmonella, Campylobacter, E. coli*, and *Enterococcus*. Findings from the pilot study were published in May 2021. In January 2019, a seafood pilot study began. This included 8 retail meat surveillance sites. Each site collected 6-8 samples of shrimp and salmon monthly. Later, sites began collecting 8 samples of tilapia. All presumptive isolates are sent to CVM's Office of Research for confirmation and further characterization, including whole genome sequencing and antimicrobial susceptibility testing. Starting in January 2020, all NARMS retail meat sites began sampling seafood (salmon, tilapia, and shrimp). This results from this pilot were included in 2019 NARMS Reports.

Phase 1 Action	Status	Accomplishment
3.2.2: Expand NARMS by monitoring antimicrobial resistance in additional bacteria species.	Complete /Ongoing[4]	The goal of this activity is to go beyond the traditional bacteria targeted in NARMS to gain a broader understanding of the ecology of resistance and its spread in the food supply. We have begun looking at resistance in foodborne *Vibrio*, *Aeromonas*, *Pseudomonas*, *Acinetobacter*, and *Staphylococcus* spp. in seafood. Beginning in October 2019, we began testing terrestrial animal samples for additional bacteria including carbapenemase-producing Enterobacterales, as well as other Gram-negative organisms, potentially including *Klebsiella*, *Citrobacter*, and *Enterobacter* spp. Samples from the 2019 a seafood pilot were cultured for the following bacteria: non-cholera *Vibrio*, *Aeromonas*, *Salmonella*, *Pseudomonas*, *Enterococcus*, *Escherichia coli*, and *Staphylococcus aureus*. Additionally, sites are using selective media to target carbapenem-resistant organisms. Resulting from this pilot study, NARMS has added *Enterococcus*, *Vibrio*, *Aeromonas* to routine seafood testing. During 2020, NARMS retail meat sites were directed to select 2 additional isolates from MacConkey agar in order to identify additional lactose positive organisms. Approximately 1,850 isolates were collected. Those isolates are being stored until resources become available for identification and subtyping.

[4] While the project may be complete in terms of collecting the data, not all data has been published yet. CVM intends to publish information as appropriate in subsequent reports once it has been have thoroughly reviewed for scientific accuracy.

Phase 1 Action	Status	Accomplishment
3.2.3: Improve our understanding of antimicrobial resistance using advanced genomic technologies and bioinformatics for research and surveillance.	Complete /Ongoing[4]	NARMS has implemented whole genome sequencing for all isolates of *Salmonella* and *Campylobacter*, and most *E. coli* recovered in the program. The sequence data are used to predict antimicrobial resistance, to compare the relatedness of strains from different sources, and to identify the genetic profiles of strains driving emergent trends in AMR. CVM is nearing completion of a metagenomic study of the animal samples collected by The Food Safety and Inspection Service and will soon be finished with a metagenomic survey of seafood products. Metagenomics refers to methods to determine the total sequence of all DNA present in a complex biological sample. This allows us to get a comprehensive view of resistance genes in a sample without being limited to cultivatable organisms. CVM completed a metagenomic survey of environmental waters, in collaboration with EPA, to evaluate antimicrobial resistance in the environment. CVM completed metagenomic studies of seafood, poultry pork and beef to gain a more complete picture of antimicrobial resistance in these commodities.

Phase 1 Action	Status	Accomplishment
3.2.4: Build and increase domestic capacity to monitor antimicrobial resistance in animal and zoonotic pathogens to include companion animals and animal feed.	Complete	1) Starting with the 2016-2018 NARMS Integrated Report, data for companion animals from Vet-LIRN's Antimicrobial Resistance Monitoring Program was included for the first time. 2) In 2020, through a research collaboration agreement with Kansas State University, NARMS analyzed 209 Enterobacterales isolates recovered from their 2018-2019 survey of swine feed mill facilities located in the Midwestern United States. Multiple antimicrobial resistance genes including *mcr-9.1* and virulence genes were identified in *Salmonella*. A recurrence of these resistant isolates in the animal feed and feed mills was observed. This highlights the potential for pathogens in a feed production environment to serve as a reservoir and transmission vehicle for antimicrobial resistance. 3) In 2021, Vet-LIRN completed a large collaborative study investigating AMR in 592 S. pseudintermedius isolates from companion animals. The study showed that genomics predicted antimicrobial resistance with 98.4 percent accuracy for thirteen different antimicrobials from 9 classes. These results clearly demonstrate the utility of genomics for assessing resistance in this pathogen, helping build our ongoing ability to monitor AMR in this important animal pathogen.
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.	Initiated/ Delayed	The final report is being prepared for publication. CVM expects the report to publish in spring 2022.

Phase 1 Action	Status	Accomplishment
3.3.2: Include genomic information and accelerate data sharing using interactive software tools and bioinformatics in NARMS reports.	Complete	1) Since 2019, NARMS retail meat susceptibility data has been uploaded into NARMS-Now quarterly while genomic data will be uploaded on a continuous basis. 2) In 2020, NARMS-Now began reporting antimicrobial sensitivity profiles based on genomic sequencing following NARMS research showing that resistance can be predicted with a high degree of accuracy from the genomic sequence. 3) State and University Laboratories that participate in FDA-NARMS began to submit genomic data directly to NCBI. Previously, laboratories submitted data to FDA-Center for Food Safety and Nutrition, which then submitted data to NCBI. This new process will reduce the time it takes for data to be shared by several days. 4) Between January 2020 and January 2021, CVM established capacity in all 23 NARMS retail meat sites to conduct whole genome sequencing (WGS) on *Salmonella, Campylobacter* and *E. coli* and to submit the data to NCBI. This work was previously done by FDA. Building this capacity in the states greatly reduces the time to data generation and enables real-time detection of emerging AMR threats. 5) NARMS-Now updates antimicrobial sensitivity profiles based on genomic sequencing of strains submitted to NCBI weekly. A tutorial on how to access NARMS data using NARMS Now is now available online for users new to the platform.
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.	Complete	Through a collaboration with the GenEpiO group and GenomeTrakr, Resistome Tracker is being enhanced by refining the metadata describing the isolate genomes in GenBank. This is mainly through a simplifying the food categories.

Where Phase 1 Falls Short - Next Steps

Overall, CVM has completed **21** out of **24** Phase 1 actions earning an **88% success rate** for implementing the 5-year plan in years 2019-2021. For the items that encountered delays, such as the publication of the Biomass Dominator and the Comprehensive AMR report, CVM is still pursuing them, along with the other initiatives expected to begin in Phase 2.

For the remainder of the 5-year plan (fiscal year 2022 – 2023), CVM intends to focus our attention on high impact items such as implementing GFI #263, solidifying an approach for defining durations of use, building an approach for collecting antimicrobial use information from food-producing animals through further exploring feasibility of public private partnership framework, and continuing to advance our AMR surveillance and monitoring programs through the activities outlined in the NARMS Strategic Plan.

Conclusion

The efforts and accomplishments highlighted in this Phase 1 report showcase a variety of topics and challenges and amplify the impact antimicrobial stewardship can have when research, surveillance, policies, and communication align. The success we have seen as part of this 5-year plan is a result of a collaborative approach with antimicrobial drug application holders, the animal agriculture industry, university researchers, federal and state partners, as well as other international and consumer advocates who have a common goal of promoting antimicrobial stewardship in veterinary settings. With new challenges ahead in Phase 2, CVM remains committed to working collaboratively with our consortium of interested stakeholders as we continue our efforts to mitigate the development of antimicrobial resistance and protect public health.

To view ongoing progress for various projects from CVM's 5-year plan beyond Phase 1, please see the FDA-TRACK: Progress on FDA's Support of Antimicrobial Stewardship in Veterinary Settings