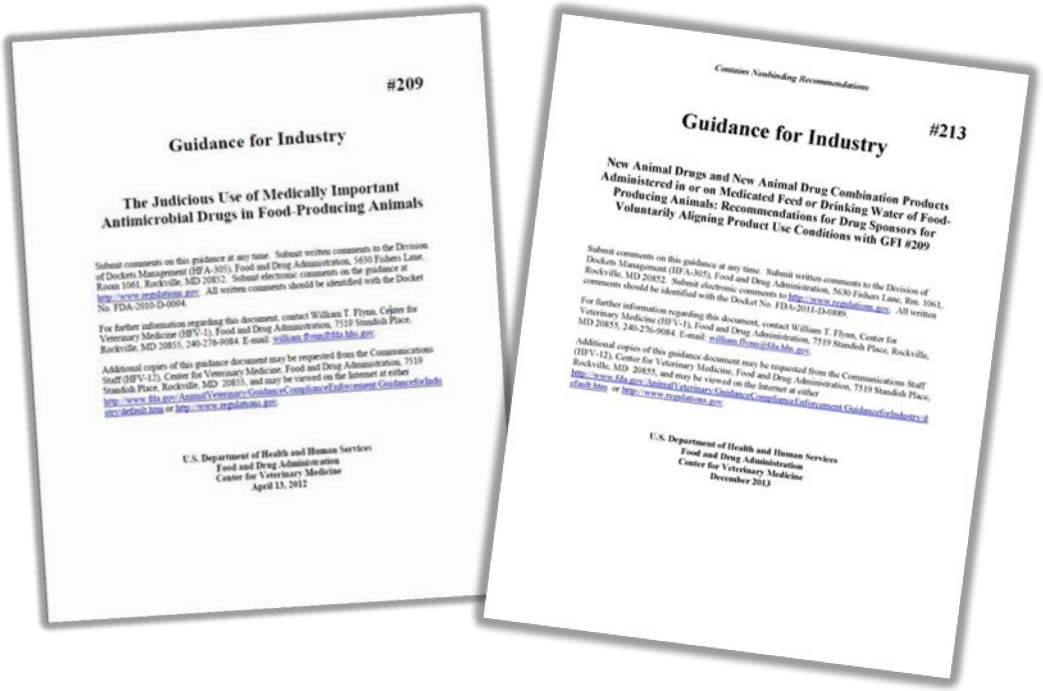
Fostering Antimicrobial Stewardship In Animals

Outline – Questions to Be Addressed

- What changes were made and why?
- What drugs are affected, which ones are not?
- What is a veterinary feed directive?
- What are key elements of VFD regulation?
- How are major or minor species impacted?
- What are next steps for fostering antimicrobial stewardship in veterinary settings?

What changes were made and why?



#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

Contains Nonbinding Recommendations

Guidance for Industry #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

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

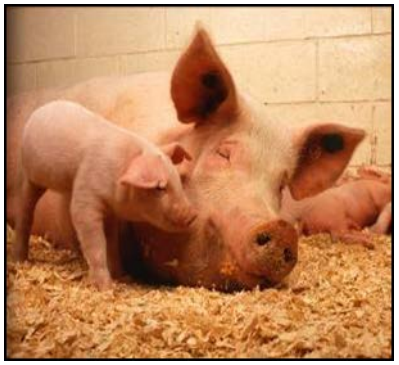
Antimicrobial Resistance – In Perspective

Complex, multi-factorial issue

- Acquired vs. naturally occurring

Use as a driver of resistance

- All uses (human, animal, horticultural, other) are part of the picture

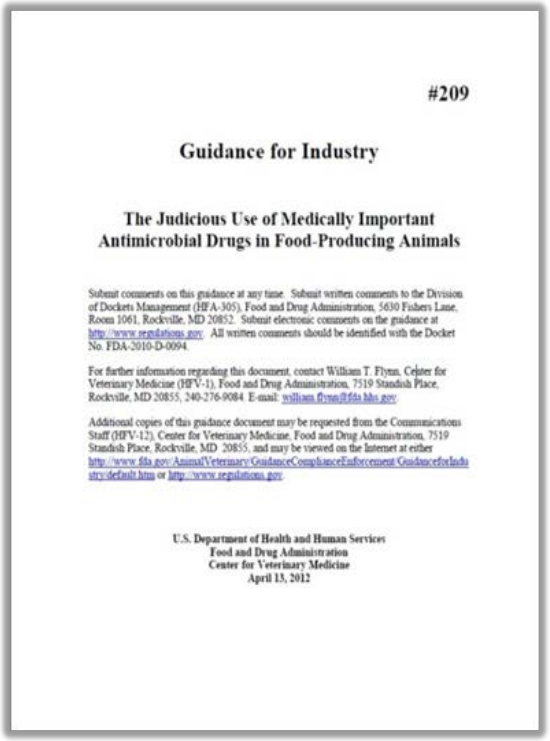



Antimicrobial Use in Animal Agriculture

- Subject of scientific and policy debate for decades
- The science continues to evolve
- Despite complexities and uncertainties steps can be identified to mitigate risk
- The intent is to implement measures that address public health concern while assuring animal health needs are met

Guidance #209:
Outlined AMR Policy

- Describes overall policy direction
  - Finalized in 2012



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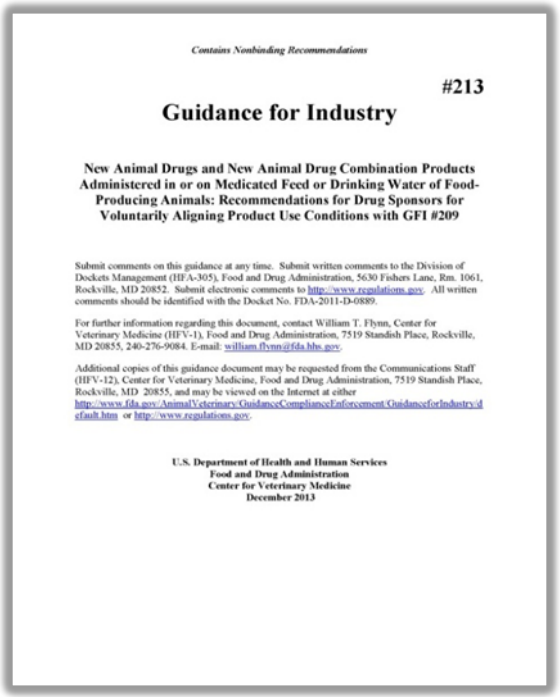
FDA's Judicious Use Strategy

- Two key principles outlined in Guidance #209
- Limit use of medically important antimicrobial drugs in food-producing animals to those uses that:
  1. are considered necessary for assuring animal health and,
  2. that include veterinary oversight or consultation

Guidance #213: Implementation

- Finalized December 2013
- More detailed guidance on implementing key principles in Guidance #209
  - Timeline
  - Defines medically important



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Guidance #213: Overview

- December 2016 - Target that was set for drug sponsors to implement changes to use conditions of medically important antimicrobials in food and water to:
  - Voluntarily withdraw approved production uses
    - such as “increased rate of weight gain” or “improved feed efficiency”
    - preserve therapeutic uses
  - Change marketing status from OTC to VFD/Rx

Guidance #213: Veterinary Oversight

- Key principle is to include veterinarian in decision-making process
  - Does not require direct veterinarian involvement in the drug administration
  - Does require use to be authorized by a licensed veterinarian in the context of a VCPR
- This means changing the marketing status from OTC to Rx or VFD
  - Water soluble products to Rx – “medicated drinking water”
  - Products used in or on feed to VFD – “medicated feed”

What drugs are affected, which ones are not?

Guidance #213:
Scope

- Only affected antimicrobials that are:
  - "Medically important"
  - Administered in feed or drinking water
    - Other dosage forms (e.g., injectable, bolus) not affected in this transition.

“Medically Important” antimicrobials

- Includes antimicrobial drugs that are considered important for therapeutic use in humans
- Guidance #213 defines “medically important” to include:
  - All antimicrobial drugs/drug classes that are listed in Appendix A of FDA’s Guidance #152 (published 2003)
  - For a complete list of affected applications see:

https://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/JudiciousUseofAntimicrobials/ucm390429.htm

“Medically Important” antimicrobials

- In reporting year 2015 -
  - approximately 74% of sales of all medically important antimicrobials were medicated feed uses.
  - approximately 21% of the sales of all medically important antimicrobials were for drinking water uses.

Affected feed-use antimicrobials

Antimicrobial Class	Specific drugs approved for use in feed
Aminoglycosides	Apramycin, Hygromycin B, Neomycin, Streptomycin
Diaminopyrimidines	Ormetoprim
Lincosamides	Lincomycin
Macrolides	Erythromycin, Oleandomycin, Tylosin
Penicillins	Penicillin
Streptogramins	Virginiamycin
Sulfas	Sulfadimethoxine, Sulfamerazine, Sulfamethazine, Sulfaquinoxaline
Tetracycline	Chlortetracycline, Oxytetracycline

Affected water-use antimicrobials

Antimicrobial Class	Specific drugs approved for use in water
Aminoglycosides	Apramycin, Gentamicin, Neomycin, Spectinomycin, Streptomycin
Lincosamides	Lincomycin
Macrolides	Carbomycin, Erythromycin, Tylosin
Penicillins	Penicillin
Sulfas	Sulfachloropyrazine, Sulfachlorpyridazine, Sulfadimethoxine, Sulfamerazine, Sulfamethazine, Sulfaquinoxaline
Tetracycline	Chlortetracycline, Oxytetracycline, Tetracycline

Drugs not affected by GFI #213

- Antimicrobials
  - that were already VFD – avilamycin, florfenicol, tilmicosin; or Rx - Tylosin.
  - that are not medically important, for example:
    - Ionophores (monensin, lasalocid, etc.)
    - Bacitracin (BMD, bacitracin zinc)
    - Bambermycins
    - Carbadox
- Other drugs (that are not antimicrobials), for example:
  - Anthelmentics: Coumaphos, Fenbendazole, Ivermectin
  - Beta agonists: Ractopamine, Zilpaterol
  - Coccidiostats: Clopidol, Decoquinate, Diclazuril

What is a veterinary feed directive?

VFD Definitions

- VFD drug
- Veterinary Feed Directive (VFD)

VFD Definitions

- VFD drug –
- (6) A "veterinary feed directive (VFD) drug" is a drug intended for use in or on animal feed which is limited by a [FDA] approved application … to use under the professional supervision of a licensed veterinarian. …

VFD Definitions

- VFD drug - …

- Use of animal feed bearing or containing a VFD drug must be authorized by a lawful veterinary feed directive.

VFD Definitions

- Veterinary Feed Directive (VFD) –
- (7) A "veterinary feed directive" is a written (nonverbal) statement issued by a licensed veterinarian in the course of the veterinarian's professional practice that orders the use of a VFD drug or combination VFD drug in or on an animal feed. …

VFD Definitions

- Veterinary Feed Directive (VFD) – …
- This written statement authorizes the client (the owner of the animal or animals or other caretaker) to obtain and use animal feed bearing or containing a VFD drug or combination VFD drug to treat the client's animals only in accordance with the conditions for use approved … by the Food and Drug Administration.

Veterinary Feed Directive

- Existing framework for veterinary oversight of feed use drugs is the veterinary feed directive (VFD)
- In 1996 Congress passed the ADAA stating that a drug intended for use in animal feed which requires professional supervision (oversight) of a licensed veterinarian is a VFD drug
- In 2000 FDA finalized regulations for authorization, distribution and use of VFDs
- Although a similar concept, (… *by or on the order of a licensed veterinarian*) VFD drugs are not Rx drugs

Updates to VFD regulation

- Changes intended to make the process more efficient while continuing to provide public health protections
- VFD Final Rule
  - June 3, 2015 – VFD final rule published
  - October 1, 2015 – VFD final rule became effective

What are key elements of VFD regulation?

Information Required on the Veterinary Feed Directive

- The regulation lists all information that must be included on the VFD in order for it to be lawful
- The veterinarian is responsible for making sure the form is complete and accurate
- See brochures for listing of required information:
  - Veterinary Feed Directive Producer Requirements
  - Veterinary Feed Directive Requirements for Distributors (Who Manufacture VFD Feed)
  - Veterinary Feed Directive Requirements for Distributors (Who Do Not Manufacture VFD Feed)
  - Veterinary Feed Directive Requirements for Veterinarians
  - Veterinary Feed Directive Requirements for Veterinarians - For Veterinary Students

VFD Final Rule: Distributors

- A ‘‘distributor’’ means any person who distributes a medicated feed containing a VFD drug to another person.
  - Such other person may be another distributor or the client-recipient of the VFD medicated feed.
- There are two kinds of distributors:
  - Only distributes VFD feed
  - Manufactures and distributes VFD Feed
- Distributors must notify FDA:
  - Prior to the first time they distribute animal feed containing a VFD drug
  - Within 30 days of any change of ownership, business name, or business address

To notify FDA, please contact:

FDA, Division of Animal Feeds
7519 Standish Place, HFV-220
Rockville, MD 20855
FAX: 240-453-6882

VFD Final Rule:
Drug Categories

- Feed-use drugs are assigned to one of two categories:
  - Category I - drugs having the lowest potential for residues
  - Category II - drugs having the highest potential for residues
- Category determines whether a facility needs to be licensed to handle the drug in the Type A form
- Definition of Category II has been revised to eliminate the automatic classification of VFD drugs into Category II

VFD Expiration Date

- VFD Expiration Date –
  - Specifies the period of time for which the VFD authorization is valid
  - A VFD feed should not be fed after the expiration date (i.e., after VFD authorization expires)
  - May be specified on the product label; if not – it cannot exceed 6 months after the date of issuance.
  - The veterinarian can use his or her medical judgment to determine whether a more limited period is warranted

Refills

- Refills (reorders) – Are only permitted to be authorized by veterinarians if the drug approval, conditional approval, or index listing expressly permits a refill (or reorder)
  - If a label is silent on refills, a refill may not be authorized
  - Currently, there are no approved VFD drugs that allow refills or reorders as a condition of their approval, conditional approval, or index listing

Approximate Number of Animals

- VFD must include an approximate number of animals:
  - The potential number of animals of the species and production class identified on the VFD that will be fed the VFD feed or combination VFD feed manufactured according to the VFD at the specified premises by the expiration date of the VFD

Approximate Number of Animals

- VFD no longer requires the amount of feed to be fed
  - Expectation is that feed mill will work with the client and veterinarian to determine an appropriate amount of feed to manufacture and distribute under the VFD
    - based on the approximate number of animals, duration of use, and expiration date

Combination VFD drugs

- **“Combination VFD drug**” - (12) A ‘‘combination veterinary feed directive (VFD) drug’’ is a combination new animal drug … intended for use in or on animal feed which is limited by a [CVM] approved application … to use under the professional supervision of a licensed veterinarian, and at least one of the new animal drugs in the combination is a VFD drug.
  - The new VFD rule requires the issuing veterinarian to include one of three “affirmation of intent” statements to affirm his or her intent as to whether the VFD drug being authorized can or cannot be used in approved combinations

Substitution of VFD drugs

- Use of an approved generic VFD drug as a substitute for an approved pioneer VFD drug in cases where the pioneer VFD drug is identified on the VFD.
  - If the veterinarian does not specify that a substitution is not allowed, the feed manufacturer may use either the approved pioneer or an approved generic VFD drug to manufacture the VFD feed.
  - However, the feed manufacturer may not substitute a generic VFD drug for a pioneer VFD drug in a combination VFD feed if the generic VFD drug is not part of an approved combination VFD drug.

Veterinary Client Patient Relationship (VCPR)

- Veterinarian issuing a VFD is required to be licensed to practice veterinary medicine and operate in compliance with either, the:
  - State-defined VCPR – if the VCPR defined by such State includes the key elements of a valid VCPR defined in § 530.3(i); or
  - Federally-defined VCPR – if a VCPR is not required to write a VFD in that state or the key elements are not met.

Veterinary Client Patient Relationship (VCPR)

The State-defined VCPR must at least address these key element concepts that the veterinarian:

1. engage with the client to assume responsibility for making clinical judgments about patient health;
2. have sufficient knowledge of the patient by virtue of patient examination and/or visits to the facility where patient is managed; and
3. provide for any necessary follow-up evaluation or care

Veterinary Client Patient Relationship (VCPR)

FDA worked with State regulatory authorities to verify whether that state has VCPR requirements in place that:

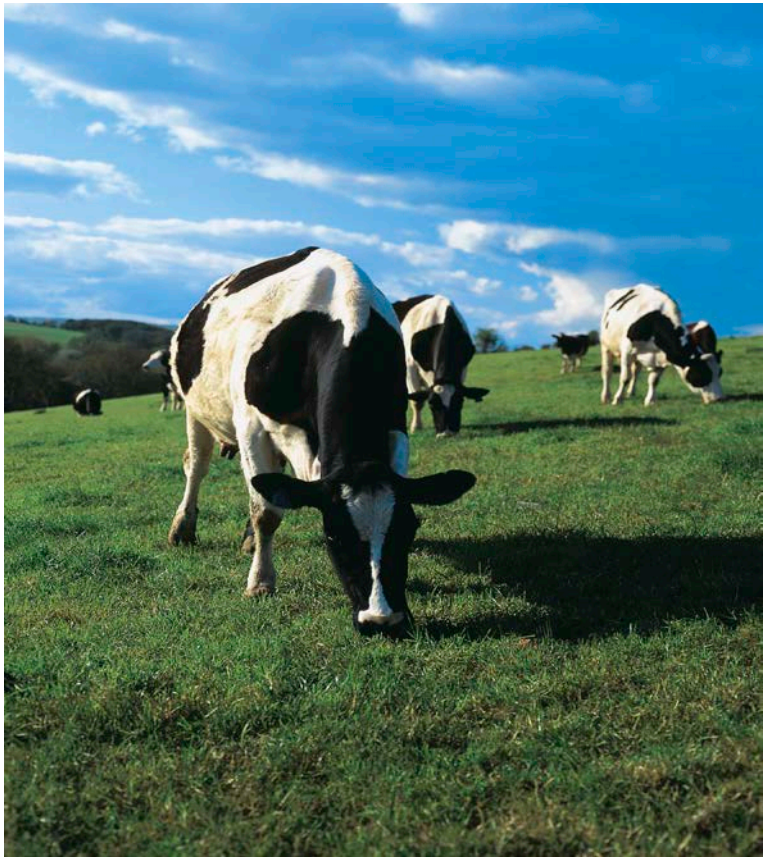
- apply to the issuance of a VFD, and
- include the key elements of the federally-defined VCPR

Veterinary Client Patient Relationship (VCPR)

FDA has provided an online list of VCPR requirements by state on the VFD website

- This list will be updated periodically as FDA receives and verifies information from states if they change their VCPR definition or its applicability
- For the current list of state or federal VCPR see https://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/ucm460406.htm

How are major or minor species impacted?



Extralabel Use (ELU)

- The Animal Medicinal Drug Use Clarification Act (AMDUCA) of 1994 and the regulations published at 21 CFR part 530 describe the requirements for, and restrictions on, extralabel drug use.

- AMDUCA amended section 512 of the FD&C Act to permit extralabel uses of drugs under certain conditions **except in animal feed**. (21 U.S.C. 360b(a)(4)(A)).

Extralabel Use

- "Extralabel use" means actual use or intended use of a drug in an animal in a manner that is not in accordance with the approved labeling.
- This includes, but is not limited to, use in species not listed in the labeling, use for indications (disease or other conditions) not listed in the labeling, use at dosage levels, frequencies, or routes of administration other than those stated in the labeling, and deviation from the labeled withdrawal time based on these different uses. (21 CFR 530.3(a)).

Extralabel Use
Compliance Policy Guide 615.115

- Because of the need to have therapeutic options available for treatment of minor species
- FDA is issued this revised CPG in December 2016
- Provides guidance to FDA staff with respect to **factors to consider when determining whether to take enforcement action** against a veterinarian, animal producer, feed manufacturer, and/or feed distributor for the extralabel use of OTC and VFD medicated feeds in minor species.

Extralabel Use-Minor Species
CPG 615.115

- Therefore, when
  - 1. there are no approved treatment options available and
  - 2. the health of animals is threatened, and
  - 3. suffering or death would result from failure to treat the affected animals,
- extralabel use of medicated feed may be **considered** for treatment of **minor species**.

Major vs Minor Species

The term ‘major species’ means **cattle**, horses, **swine**, **chickens, turkeys**, dogs, and cats, … 21 U.S.C. 321 (nn)

The term ‘minor species’ means animals other than humans that are not major species. 21 U.S.C. 321 (oo)

Extralabel Use
CPG 615.115

- In general, the Agency **will not recommend** or initiate **enforcement action** against

  - the veterinarian,
  - animal producer,
  - feed mill, or other distributor

  when extralabel use is **consistent with this document.** (CPG 615.115)

Extralabel Use
CPG 615.115

- Applies to VFD and OTC medicated feed products
- Includes a number of considerations for
  - Veterinarians
  - Producers
  - Distributors/Manufacturers
- Suggest review CPG carefully

http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-afda-ice/documents/webcontent/ucm074659.pdf

When did this go in effect?

Implementation Timeline Summary

- October 1, 2015 – Updated VFD regulation went into effect
- January 1, 2017 –
  - As of this date, all medically important antimicrobials for use in or on feed require a VFD and those for use in drinking water require a Rx
  - And, it is no longer legal to use these drugs for production (growth promotion) purposes

Changes to Affected Products

Of the **292** new animal drug applications initially affected by **Guidance for Industry #213**:

— **84** were completely withdrawn

Of the remaining **208** applications,

- **93** applications – oral dosage form – converted from OTC to Rx
- **115** applications – medicated feed – converted from OTC to VFD

—Production (e.g., growth promotion) indications were withdrawn from all applications that included such indications for use

What are next steps for fostering antimicrobial stewardship in veterinary settings?

Important areas of focus include:

- Align products - Align approved use conditions of medically important antimicrobial products with judicious use principles
- Use practices – Implement/reinforce antimicrobial stewardship in all veterinary settings
- Monitor progress - Enhance monitoring of antimicrobial resistance and antimicrobial drug use in animals

Align medically important antimicrobials with judicious use principles

A focus for FDA - making sure the labeled use conditions of medically important antimicrobials are consistent with judicious use/stewardship principles

- Changes implemented through Guidance #213 process are critically important steps forward, but we believe additional measures are needed.

Align medically important antimicrobials with judicious use principles

Additional measures include:

- Examine those for feed/water uses that do not currently have an explicitly defined duration of dosing
- Develop strategy and timeline for bringing all dosage forms of medically important antimicrobials under veterinary oversight
- Additional focus on promoting antimicrobial stewardship in companion animals

Implement/reinforce antimicrobial stewardship in all veterinary settings

Many organizations and affected stakeholders have role to play in supporting progress in this area

- Involvement of multiple Federal agencies including FDA, USDA, and CDC
- Veterinary and animal producer organizations play key role
- State agencies that oversee licensing/practice standards

<u>Challenges</u>

- Diversity of settings
- Coordinating activities across affected stakeholders

Implement/reinforce antimicrobial stewardship in all veterinary settings

Progress to date includes:

- A broad array of organizations have actively supported implementation of Guidance #213 changes
  - Webinars, public meetings, brochures, guidance documents, other web-based materials
- Academic organizations are incorporating judicious use principles into curricula at veterinary and land grant colleges
- Veterinary organizations, including State veterinary boards, are re-examining and updating policies
- Industry “quality assurance programs” include elements regarding the judicious use of antimicrobials

Enhance monitoring of antimicrobial resistance and antimicrobial drug use

- As we implement judicious use strategies, it is important that we collect sufficient data to assess the impact of such strategies
  - "Success" should not focus solely on reductions in overall sales or use
  - It is important that we identify appropriate indicators that help us assess the extent to which judicious use/stewardship plans are being implemented
- Our ultimate goal is that improved use practices will curb resistance development

Enhance monitoring of antimicrobial resistance and antimicrobial drug use

Challenges include:

- Wide diversity of settings where antimicrobials are used
- Substantial differences in “health care” infrastructure compared to human health care
- Lack of new funding has delayed progress on enhanced data collection

Progress being made:

- USDA preparing to conduct antimicrobial use surveys
- Utilizing existing funds, FDA recently awarded two grants

In Closing…

Significant progress has been made; changes implemented January 1 was important milestone

Judicious use/stewardship of antimicrobials is an ongoing process impacting many stakeholders and sectors; incremental steps are needed to phase in changes

Continued engagement of veterinary community, animal producers, and others is critical

While optimizing use is important; development of alternative products and disease management strategies to reduce the need for antimicrobials is also an important priority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