



# Medically Important Antibiotics in Animal Agriculture

Craig Lewis, DVM MPH  
Office of the Director  
Center for Veterinary Medicine

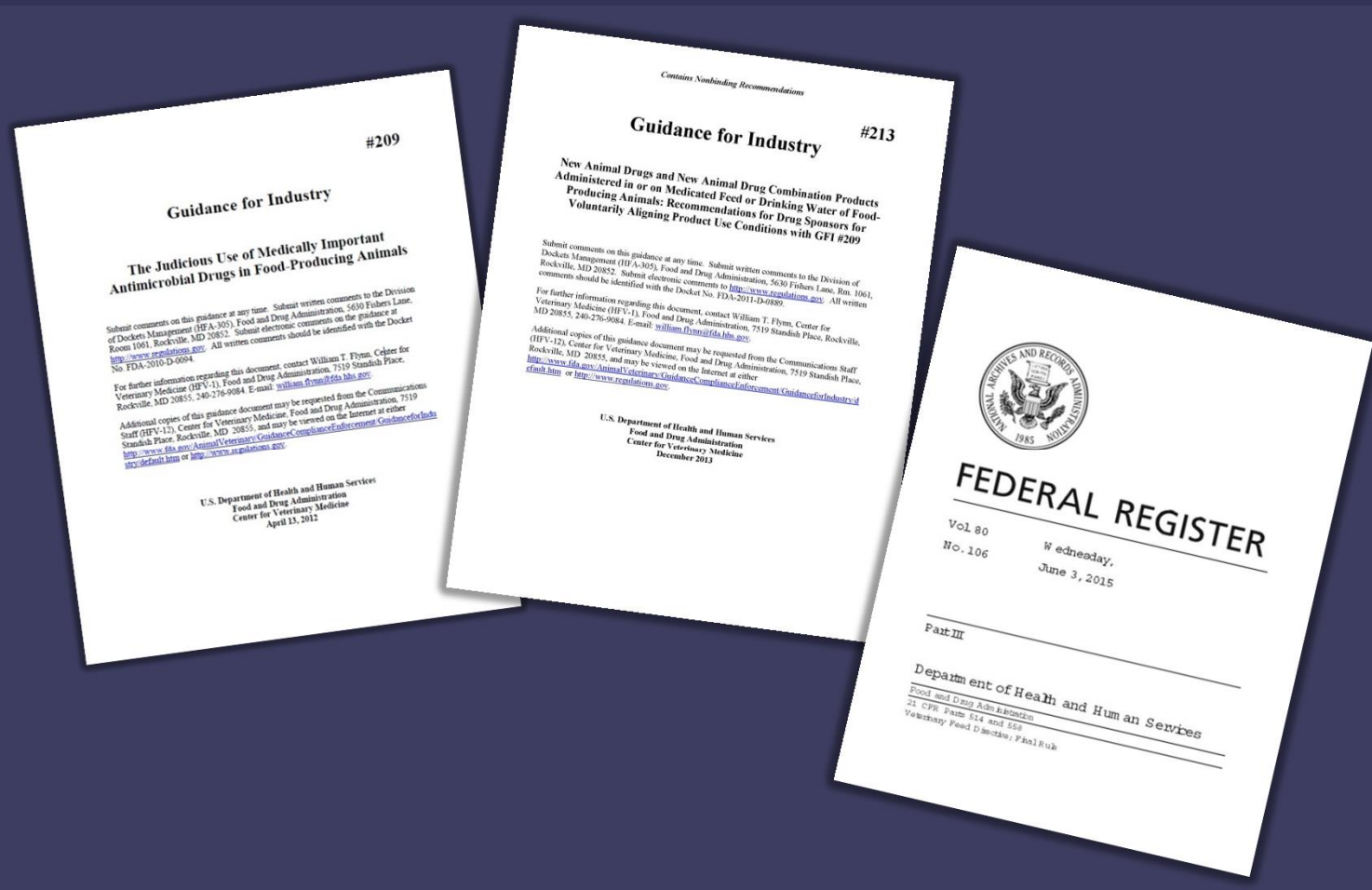
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## Outline . Questions to Be Addressed

- What changes are being made and why?
- What drugs are affected, which ones are not?
- What is a veterinary feed directive?
- What are key elements of VFD regulation?
- When will this go into effect?

# What changes are being made and why?



# 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



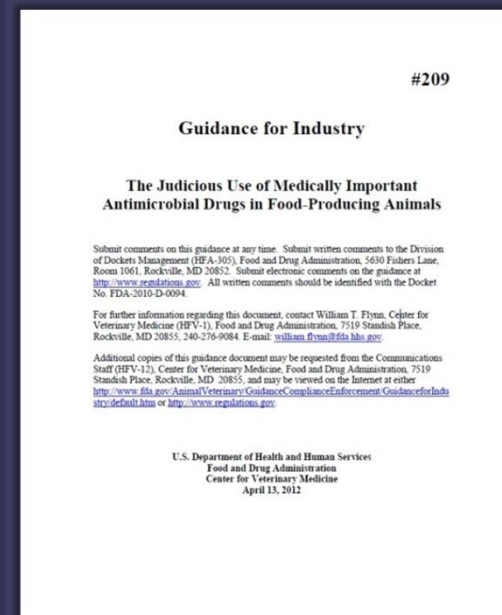


# Antibiotic Use in Animal Agriculture

- Subject of scientific and policy debate for decades
- The science continues to evolve
- Despite complexities and uncertainties steps can be identified to mitigate risk
- 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





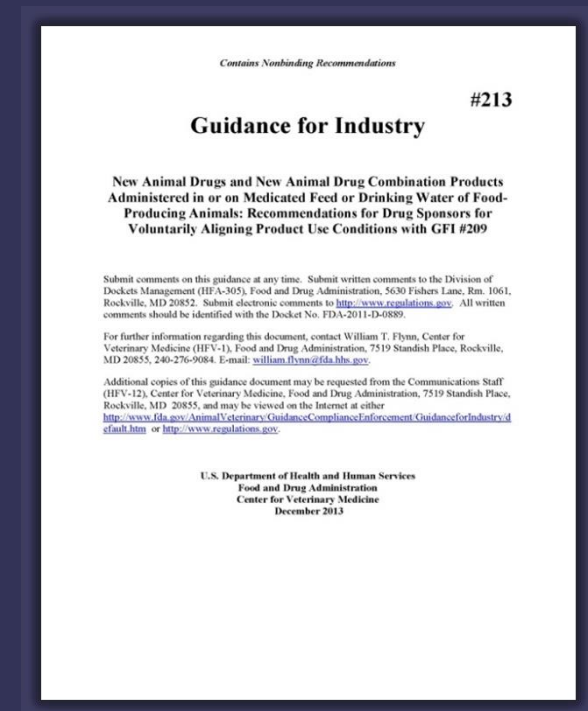
## FDA's Judicious Use Strategy

Two key principles outlined in Guidance #209:

1. Limit medically important antimicrobial drugs to therapeutic purposes (i.e., those uses considered necessary for ensuring animal health)
2. Require veterinary oversight or consultation for such therapeutic uses in food-producing animals

# Guidance #213: Implementation

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





# Guidance #213: Overview

- December 2016 - Target for drug sponsors to implement changes to use conditions of medically important antibiotics in food and water to:
  - Withdraw approved production uses
    - such as %~~an~~ increased rate of weight gain+or  
%~~an~~ improved feed efficiency+
  - Such production uses will no longer be legal

## Guidance #213: Removing Production Uses

- However, therapeutic uses are to be retained
  - treatment, control, and prevention indications
- Require veterinary oversight

# Guidance #213: Veterinary Oversight

- Key principle is to include veterinarian in decision-making process
  - Does not require direct veterinarian involvement in drug administration
  - Does require use be authorized by licensed veterinarian
- This means changing marketing status from OTC to Rx or VFD
  - Water soluble products to Rx . %medicated water+
  - Products used in or on feed to VFD . %medicated feed+

# What drugs are affected, which ones are not?



## Guidance #213: Scope

- Only affects antibiotics that are:
  - Medically important+
  - Administered in feed or drinking water
    - Other dosage forms (e.g., injectable, bolus) not affected

## Medically Important antibiotics

- 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

# Affected feed-use antibiotics

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 antibiotics

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



# Drugs not affected by Guidance #213

## ■ Antibiotics

- that are 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 antibiotics), including:

- Anthelmintics: 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 ~~u~~veterinary feed directive (VFD) drug is a 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.

# VFD Definitions

- **VFD drug - ò**
- 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 ~~u~~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. ò

# VFD Definitions

- **Veterinary Feed Directive (VFD)** . ã
- 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 ã 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 Federal Law stating that medicated feeds which require veterinary oversight are VFDs
- 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*) VFDs are not Rx



# Updates to VFD regulation

- Changes intended to make 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

# Current VFD Drugs

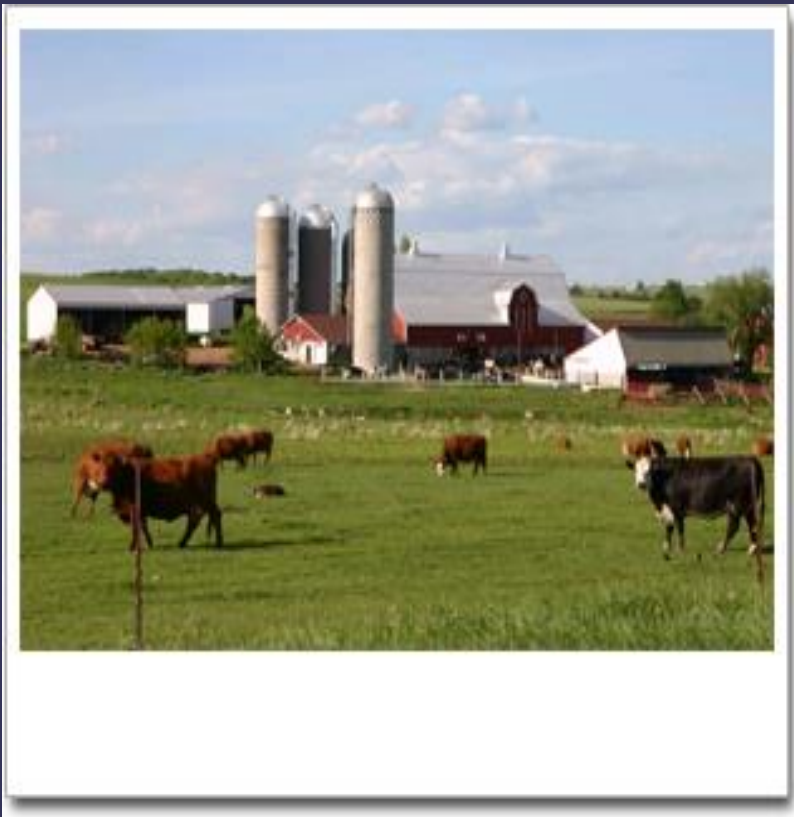
Currently Approved VFD Drugs	Approved for Use in the Following Species
Avilamycin	Swine . reduction of diarrhea . E. coli.
Florfenicol	Fish . control of mortality (various diseases by fish type) Swine . control of SRD
Tilmicosin	Cattle . control of BRD Swine . control of SRD

**Note:** Only the drugs that are currently approved as VFD drugs (above) are affected by the new VFD regulation (went into effect on October 1, 2015).

# Examples of medicated feed-use antibiotics that are expected to transition to VFD status

Antimicrobial Class	Specific drugs approved for use in feed
Aminoglycosides	Apramycin, <i>Neomycin</i> , Streptomycin
Diaminopyrimidines	Ormetoprim
Hygromycin B	Hygromycin B
Lincosamides	<i>Lincomycin</i>
Macrolides	Erythromycin, <u>Oleandomycin</u> , <i>Tylosin</i>
Penicillins	<u>Penicillin - Currently only production uses.</u>
Streptogramins	<i>Virginiamycin</i>
Sulfas	Sulfadimethoxine, Sulfamerazine, Sulfamethazine, Sulfaquinoxaline
Tetracycline	<i>Chlortetracycline</i> , <i>Oxytetracycline</i>

# What are key elements of VFD regulation?



## Information Required on VFD Form

- Regulation lists all information that must be included on VFD in order for it to be lawful
- Veterinarian is responsible for making sure the form is complete and accurate
- See brochures for listing of required information

# 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:

1. Only distributes VFD feed
2. 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

# 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
- This change applies to the existing approved VFD drug products, in addition to the products that will become VFD under GFI #213

# Expiration Date and Duration of Use

## ■ 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



# Expiration Date and Duration of Use

## ■ The Duration of Use –

- A separate concept from the expiration date
- The length of time that the animal feed containing the VFD drug is allowed to be fed to the animals
- Established as part of the approval, conditional approval, or index listing process
- If the VFD order will expire before completing the duration of use on the order, the client should contact his/her veterinarian to request a new VFD order

# Current VFD Drugs

Currently Approved VFD Drugs	Approved for Use in the Following Species	VFD Expiration Date	Duration of Use
Avilamycin	Swine . reduction of diarrhea . E. coli.	42 d	21 d
Florfenicol	Fish . control of mortality (various diseases by fish type)	15 d	10 d
	Swine . control of SRD	90 d	5 d
Tilmicosin	Swine . control of SRD	90 d	21 d
	Cattle . control of BRD	45 d	14 d

# Medically important antibiotics used in animal feed expected to transition from OTC to VFD marketing status.

- VFD Expiration Date: not to exceed 6 months
- Duration of Use: See CVM Blue Bird Label website
- <http://www.fda.gov/animalveterinary/products/animalfoodfeeds/medicatedfeed/bluebirdlabels/default.htm>

# Refills

- Refills (reorders) . Are only permitted to be issued by veterinarians if the drug approval, conditional approval, or index listing expressly allows 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 will no longer be required to specify 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
  - Expect that this will be addressed through inclusion of a check box on the VFD form

# Current VFD Drugs

Currently Approved VFD Drugs	Approved for Use in the Following Species	Combinations/ Affirmation
Avilamycin	Swine . reduction of diarrhea . E. coli.	None/ 1
Florfenicol	Fish . control of mortality (various diseases by fish type)	None/ 1
	Swine . control of SRD	None/ 1
Tilmicosin	Swine . control of SRD	None/ 1



# Current VFD Drugs

<b>Currently Approved VFD Drug</b>	<b>Currently Approved Combination</b>	<b>Approved for Use in the Following Species</b>	<b>Affirmation</b>
Tilmicosin	Tilmicosin only	Cattle . control of BRD	1
	+ Monensin	Cattle . control of BRD + Coccidiosis	2 or 3
	+ Monensin	Cattle . control of BRD + Feed efficiency	2 or 3

## 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.

# Current VFD Drugs

Currently Approved VFD Drugs	Approved for Use in the Following Species	Pioneer	Generic
Avilamycin	Swine . reduction of diarrhea . E. coli.	Yes	NA
Florfenicol	Fish . control of mortality (various diseases by fish type)	Yes	NA
	Swine . control of SRD	Yes	NA
Tilmicosin	<b>Swine – control of SRD</b>	<b>Yes</b>	<b>Yes</b>
		Substitution Option	
	Cattle . control of BRD	Yes	NA

## Veterinary Client Patient Relationship (VCPR)

- Veterinarian issuing a VFD is required to be licensed to practice veterinary medicine and operate in compliance with either:
  - **State-defined VCPR** . if VCPR defined by such State includes the key elements of a valid VCPR defined in § 530.3(i); or
  - **Federally-defined VCPR** - where no applicable or appropriate State VCPR requirements exist

# Veterinary Client Patient Relationship (VCPR)

- The State-defined VCPR must at least address the 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 has worked with (and continues to work 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)

- A list of VCPR by state is posted on CVM's VFD Website

- <http://www.fda.gov/animalveterinary/developmentapprovalprocess/ucm071807.htm>

- This list will be updated periodically as FDA receives and verifies information from states if they change their VCPR definition or its applicability

When will this go into effect?





# Implementation Timeline Summary

- **October 1, 2015** . VFD Final Rule went into effect
  - Applies to current VFD drugs
- **January 1, 2017** . Target for all medically important antimicrobials for use in or on feed to require a VFD
  - December 2016 . Target for drug sponsors to implement changes to use conditions of products affected by GFI #213

## Ongoing activities/Next steps

- Develop guidance on format of VFD template
- Updates:
  - GFIs # 120 (VFD Rule) and # 181 (Blue Bird Labels) are now posted on CVM's website.

# References and Resources

- **See Veterinary Feed Directive and Judicious Use CVM/FDA Sources of Information - In your packet.**

Thank You

