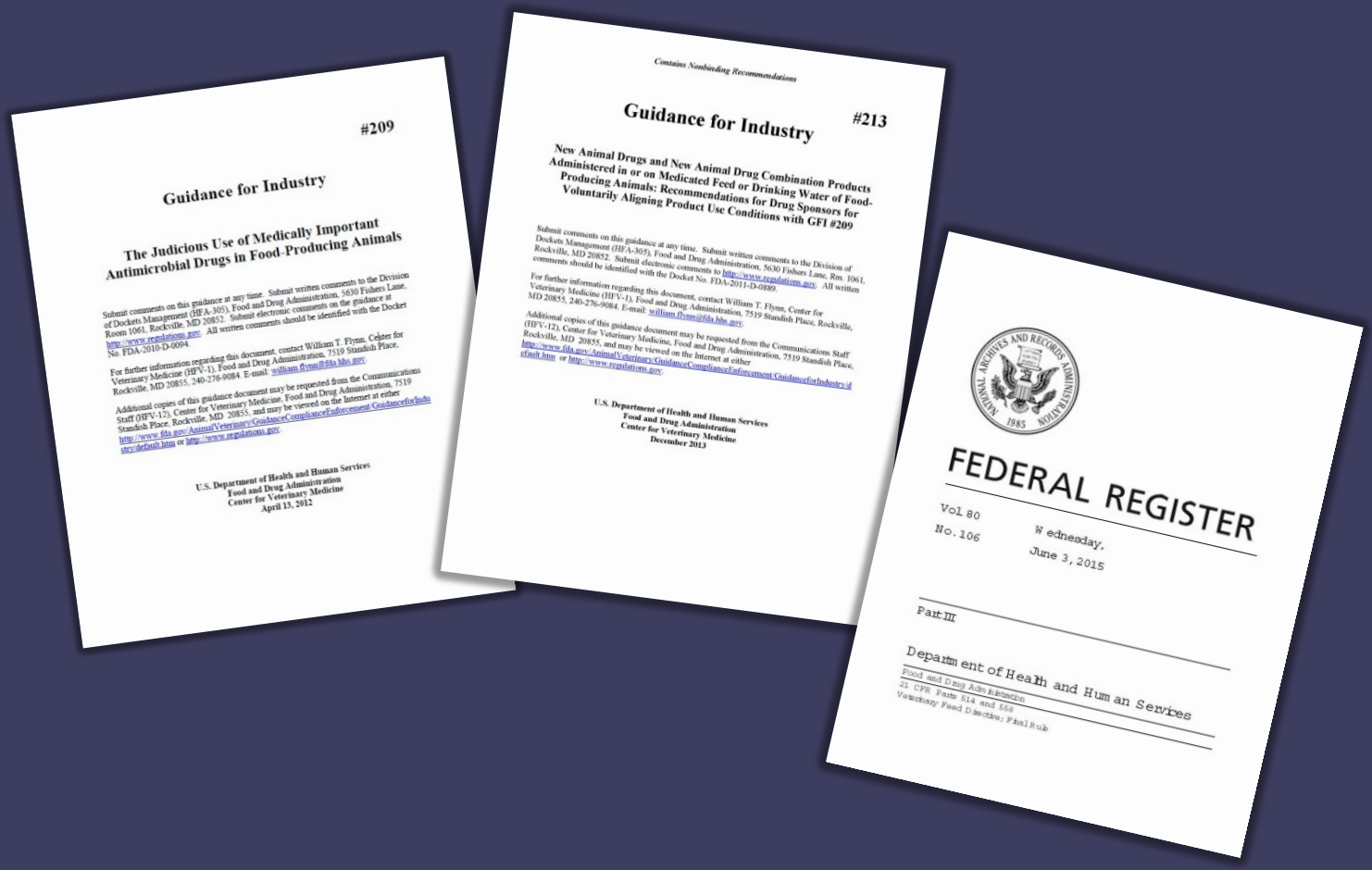
Medically Important Antimicrobials in Animal Agriculture

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?



#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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December 2013

NATIONAL ARCHIVES AND RECORDS ADMINISTRATION 1985

FEDERAL REGISTER

Vol. 80 No. 106 Wednesday, June 3, 2015

Part III

Department of Health and Human Services

Food and Drug Administration

21 CFR Parts 514 and 558

Veterinary Feed Directive; Final Rule

Antimicrobial Resistance – In Perspective

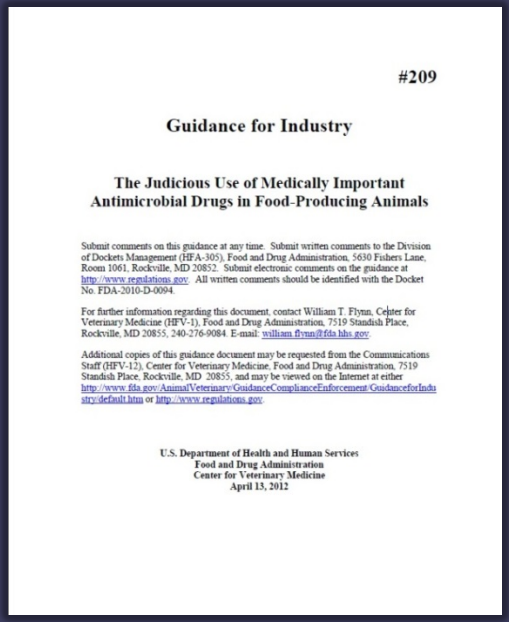
- Complex, multi-factorial issue
  - Acquired vs. naturally occurring
- Use as a driver of resistance
  - All uses (human, animal, horticultural, other) are part of the picture

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



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FDA's Judicious Use Strategy

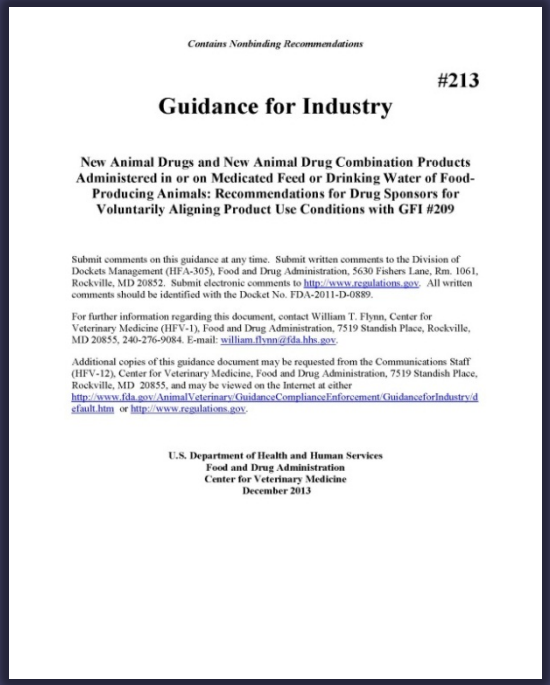
Two key principles outlined in Guidance #209:

Limit use of medically important antimicrobial drugs in food-producing animals to those uses

1. considered necessary for assuring animal health. (therapeutic uses)
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 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”
  - After the label changes these production uses will no longer be legal

Guidance #213: Overview

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

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 affects antimicrobials that are:
  - "Medically important"
  - Administered in feed or drinking water
    - Other dosage forms (e.g., injectable, bolus) <u>not</u> 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
  - For a complete list of affected applications see:

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

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 Guidance #213

- Antimicrobials
  - 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 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 [CVM] 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

Current VFD Drugs

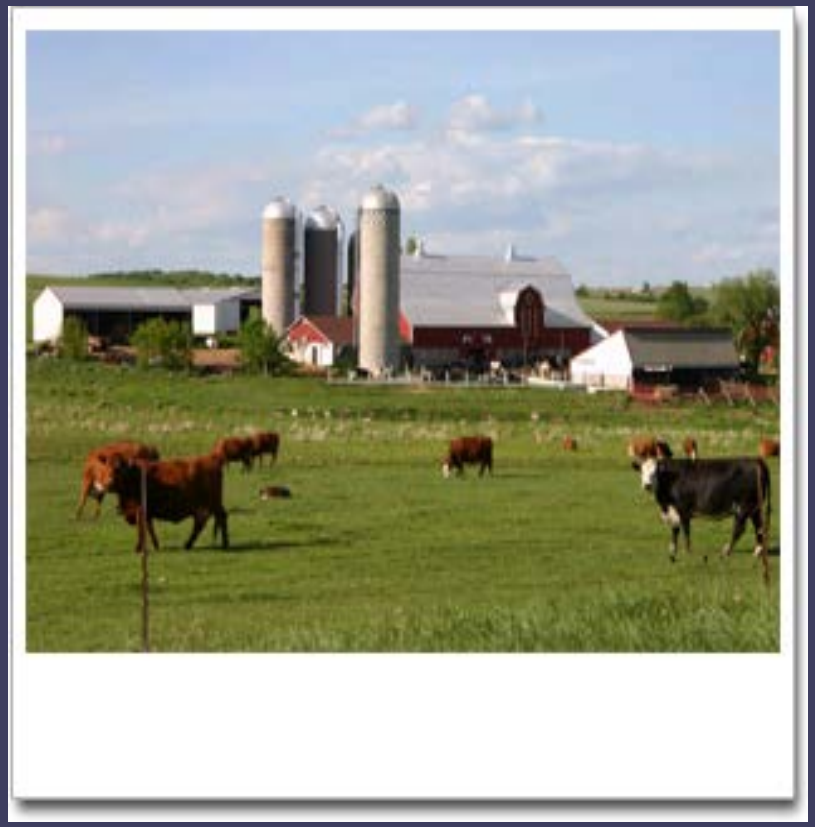
Currently Approved VFD Drugs	Approved for Use in the Following Species
Avilamycin	Swine – reduction of diarrhea – E. coli.
Florfenicol	Fish – control of mortality (various diseases by fish type) Swine – control of SRD
Tilmicosin	Cattle – control of BRD Swine – control of SRD

Note: The three drugs above are affected by the VFD regulation which went into effect 1 October 2015, because they are currently approved as VFD drugs. The medically important antimicrobials will be affected by the VFD Rule when they transition from OTC to VFD beginning 1 January 2017. (See the next slide.)

Examples of medicated feed-use antimicrobials that are expected to **be voluntarily withdrawn or** transition **from OTC** to VFD status

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

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:

  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

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

VFD Expiration Date and Duration of Use

- **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

VFD 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 the Following Uses	VFD Expiration Date	Duration of Use
Avilamycin	Swine – reduction of diarrhea – E. coli.	90 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 antimicrobials used in animal feed expected to transition from OTC to VFD marketing status.

- 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 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

Current VFD Drugs

Currently Approved VFD Drugs	Approved for Use in the Following Species – abbreviated indication	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

Currently Approved VFD Drug	Currently Approved Combination	Approved for Use in the Following Species - abbreviated indication	Affirmation
Tilmicosin (pioneer)	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 Drug	Approved for Use in the Following Species - abbreviated indication	Pioneer	Generic
Avilamycin	Swine – reduction if diarrhea – E. coli	Yes	No
Florfenicol	Fish – control of mortality (various diseases by fish type)	Yes	No
	Swine – control of SRD	Yes	No
Tilmicosin	**Swine – control of SRD**	**Yes**	**Yes**
		Substitution Option	
	Cattle – control of BRD	Yes	No

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 http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/ucm460406.htm

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 implementation that all medically important antimicrobials for use in or on feed to require a VFD and for those for use in drinking water to require a Rx
  - December 2016 – Target for drug sponsors to implement changes to use conditions of products affected by GFI #213

References and Resources

NOTE:

- **As the industry transitions, CVM anticipates additional changes during the coming months to the information in this presentation, please check the following links for the most recent updates.**

References and Resources

- **Veterinary Feed Directive,** http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/ucm071807.htm
- **Judicious Use,** http://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/JudiciousUseofAntimicrobials/default.htm
- **Blue Bird Labels,** http://www.fda.gov/AnimalVeterinary/Products/AnimalFoodFeeds/MedicatedFeed/BlueBirdLabels/default.htm

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