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?
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:

Limit use of medically important antimicrobial drugs in food-producing animal 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
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 “increased rate of weight gain” or “improved feed efficiency”
  - After the label changes these production uses will no longer be legal
Guidance #213: Removing Production Uses

- However, therapeutic uses are to be retained
- treatment, control, and prevention indications
- Requires 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 drug administration
  - Does require use 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 antibiotics that are:
  - “Medically important”
  - Administered in feed or drinking water

- Other dosage forms (e.g., injectable, bolus) not affected in this transition.
“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
  - For a complete list of affected applications see:
    - [http://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/JudiciousUseofAntimicrobials/ucm390429.htm](http://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/JudiciousUseofAntimicrobials/ucm390429.htm)
### Affected feed-use antibiotics

<table>
<thead>
<tr>
<th>Antimicrobial Class</th>
<th>Specific drugs approved for use in feed</th>
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<tbody>
<tr>
<td>Aminoglycosides</td>
<td>Apramycin, Hygromycin B, Neomycin, Streptomycin</td>
</tr>
<tr>
<td>Diaminopyrimidines</td>
<td>Ormetoprim</td>
</tr>
<tr>
<td>Lincosamides</td>
<td>Lincomycin</td>
</tr>
<tr>
<td>Macrolides</td>
<td>Erythromycin, Oleandomycin, Tylosin</td>
</tr>
<tr>
<td>Penicillins</td>
<td>Penicillin</td>
</tr>
<tr>
<td>Streptogramins</td>
<td>Virginiamycin</td>
</tr>
<tr>
<td>Sulfas</td>
<td>Sulfadimethoxine, Sulfamerazine, Sulfamethazine, Sulfaquinoxaline</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Chlortetracycline, Oxytetracycline</td>
</tr>
</tbody>
</table>
Affected **water-use** antibiotics

<table>
<thead>
<tr>
<th>Antimicrobial Class</th>
<th>Specific drugs approved for use in water</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>Apramycin, Gentamicin, Neomycin, Spectinomycin, Streptomycin</td>
</tr>
<tr>
<td>Lincosamides</td>
<td>Lincomycin</td>
</tr>
<tr>
<td>Macrolides</td>
<td>Carbomycin, Erythromycin, <strong>Tylosin</strong></td>
</tr>
<tr>
<td>Penicillins</td>
<td>Penicillin</td>
</tr>
<tr>
<td>Sulfas</td>
<td>Sulfachloropyrazine, Sulfachlorpyridazine, Sulfadimethoxine, Sulfamerazine, Sulfamethazine, Sulfquinoloxaline</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Chlortetracycline, Oxytetracycline, Tetracycline</td>
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</table>
Drugs not transitioning from OTC to VFD under 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:**
  - 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

- The framework for veterinary oversight of feed use drugs is the veterinary feed directive (VFD) rule.

- 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)* VFD drugs are not Rx drugs.
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

<table>
<thead>
<tr>
<th>Currently Approved VFD Drugs</th>
<th>Approved for Use in the Following Species</th>
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<tbody>
<tr>
<td>Avilamycin</td>
<td>Swine – reduction of diarrhea – E. coli.</td>
</tr>
<tr>
<td>Florfenicol</td>
<td>Fish – control of mortality (various diseases by fish type)</td>
</tr>
<tr>
<td></td>
<td>Swine – control of SRD</td>
</tr>
<tr>
<td>Tilmicosin</td>
<td>Cattle – control of BRD</td>
</tr>
<tr>
<td></td>
<td>Swine – control of SRD</td>
</tr>
</tbody>
</table>

**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 antibiotics that are expected to **be withdrawn or transition from OTC to VFD status**

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<td>Macrolides</td>
<td>Erythromycin, <em>Oleandomycin</em>, <em>Tylosin</em></td>
</tr>
<tr>
<td>Penicillins</td>
<td>Penicillin - Currently only production uses.</td>
</tr>
<tr>
<td>Streptogramins</td>
<td><em>Virginiamycin</em></td>
</tr>
<tr>
<td>Sulfas</td>
<td>Sulfadimethoxine, Sulfamerazine, Sulfamethazine, Sulfadoxine</td>
</tr>
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<td>Tetracycline</td>
<td><em>Chlortetracycline</em>, <em>Oxytetracycline</em></td>
</tr>
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</table>
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 directive 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
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

<table>
<thead>
<tr>
<th>Currently Approved VFD Drugs</th>
<th>Approved for the Following Uses – (abbreviated indications)</th>
<th>VFD Expiration Date</th>
<th>Duration of Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avilamycin</td>
<td>Swine – reduction of diarrhea – E. coli.</td>
<td>90 d</td>
<td>21 d</td>
</tr>
<tr>
<td>Florfenicol</td>
<td>Fish – control of mortality (various diseases by fish type)</td>
<td>≤ 6 m</td>
<td>10 d</td>
</tr>
<tr>
<td></td>
<td>Swine – control of SRD</td>
<td>90 d</td>
<td>5 d</td>
</tr>
<tr>
<td>Tilmicosin</td>
<td>Swine – control of SRD</td>
<td>90 d</td>
<td>21 d</td>
</tr>
<tr>
<td></td>
<td>Cattle – control of BRD</td>
<td>45 d</td>
<td>14 d</td>
</tr>
</tbody>
</table>
Medically important antibiotics 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 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
## Current VFD Drugs

<table>
<thead>
<tr>
<th>Currently Approved VFD Drugs</th>
<th>Approved for Use in the Following Species – (abbreviated indications)</th>
<th>Combinations/ Affirmation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avilamycin</td>
<td>Swine – reduction of diarrhea – E. coli.</td>
<td>None/ 1</td>
</tr>
<tr>
<td>Florfenicol</td>
<td>Fish – control of mortality (various diseases by fish type)</td>
<td>None/ 1</td>
</tr>
<tr>
<td></td>
<td>Swine – control of SRD</td>
<td>None/ 1</td>
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<tr>
<td>Tilmicosin</td>
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<td>None/ 1</td>
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# Current VFD Drugs

<table>
<thead>
<tr>
<th>Currently Approved VFD Drug</th>
<th>Currently Approved Combination</th>
<th>Approved for Use in the Following Species – (abbreviated indication)</th>
<th>Affirmation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tilmicosin</td>
<td>Tilmicosin only</td>
<td>Cattle – control of BRD</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>+ Monensin</td>
<td>Cattle – control of BRD + Coccidiosis</td>
<td>2 or 3</td>
</tr>
<tr>
<td></td>
<td>+ Monensin</td>
<td>Cattle – control of BRD + Feed efficiency</td>
<td>2 or 3</td>
</tr>
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</table>
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

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<tr>
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<th>Approved for Use in the Following Species</th>
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<th>Generic</th>
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<tr>
<td>Avilamycin</td>
<td>Swine – reduction of diarrhea – E. coli.</td>
<td>Yes</td>
<td>NA</td>
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<td>Florfenicol</td>
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<td>Yes</td>
<td><strong>Yes</strong></td>
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<td></td>
<td>Cattle – control of BRD</td>
<td>Yes</td>
<td>NA</td>
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Substitution Option
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** - 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 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 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 such states 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/ucm071807.htm](http://www.fda.gov/animalveterinary/developmentapprovalprocess/ucm071807.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 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
References and Resources

- **NOTE:**

- As the industry transitions, CVM anticipates several 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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  - CVM FR Notices:
    Federal Register notices issued by the Center for Veterinary Medicine, excluding drug approvals.
  - What's New:
    RSS Feed for new items posted to the Animal & Veterinary section of FDA's website.
Thank You