Current Antibiotic Issues and Overview of the New Veterinary Feed Directive (VFD)

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Beef Technical Consultant
Grain & Feed Industry Conference

1/13/16
WHY
WE DO
WHAT WE DO

Empowering Others
Overview

- Consumer attitudes
- Access to antibiotics
- VFD implementation timeline
- Final VFD rules
- Implementing a VFD
- Electronic VFDs
- Impact on Elanco
Consumer Attitudes
Consumer Attitudes

• Antibiotic use is a public health issue

• Important for animal agriculture to:
  – Be proactive & take a leading role
  – Maintain confidence in food supply
  – Build consumer trust

<table>
<thead>
<tr>
<th>Consumer attitudes*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>48%</strong></td>
</tr>
<tr>
<td>Feel <strong>uncomfortable</strong> about antibiotic use in animal production</td>
</tr>
</tbody>
</table>

<p>| |</p>
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>71%</strong></td>
</tr>
<tr>
<td>Have “<strong>serious or some concerns</strong>” about conventional methods</td>
</tr>
</tbody>
</table>

<p>| |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>53%</strong></td>
</tr>
<tr>
<td>Frequently <strong>wonder</strong> if the food they buy is safe</td>
</tr>
</tbody>
</table>

* Source: ml&p research for USFRA, 10/11, n=1,400.
## Consumer Attitudes

<table>
<thead>
<tr>
<th>You say</th>
<th>They hear</th>
</tr>
</thead>
<tbody>
<tr>
<td>We use antibiotics to be more efficient</td>
<td>Because you only care about making money</td>
</tr>
<tr>
<td>We use antibiotics to keep animals healthy</td>
<td>You HAVE to use antibiotics because animals are kept in poor conditions</td>
</tr>
<tr>
<td>Regulatory agency reviews have approved antibiotics as safe after rigorous review process</td>
<td>We don’t know if it’s safe for the long term. They’ve been wrong before.</td>
</tr>
<tr>
<td>There are rules that dictate maximum residue limits allowed in animals</td>
<td>How can we be sure ANY residue is safe?</td>
</tr>
<tr>
<td>There is no evidence that use of antibiotics in animals causes resistance in humans</td>
<td>Yeah, right. We’re using so many, that has to be part of the reason.</td>
</tr>
</tbody>
</table>
Access to Antibiotics
Access to Antibiotics

- A public health issue
- Access to effective antibiotics:

  Critical for public health
  Vital for livestock & poultry production
  Essential for animal well-being
Access to Antibiotics

• U.S. Food and Drug Administration:
  – Concerned overuse in animals may reduce effectiveness in humans
  – Is making important changes to antibiotic use in animals
  – Goal is to promote judicious use of antibiotics, protect public health, and help curb the development of antimicrobial resistance
Access to Antibiotics

- FDA issues 3 documents proposing to modify use of medically important antibiotics in food-producing animals

Guidance for Industry (GFI) #209

Guidance for Industry (GFI) #213

CFR 558
**Guidance for Industry #209**

- The “what” component
- Establishes “judicious use” principle
  - Limits shared-class antibiotics to therapeutic purposes
- Key: Use of **medically important** antimicrobial drugs in food-producing animals should be limited to:

1. Uses necessary to assure animal health
   - Prevention
   - Control
   - Treatment

2. Uses that include veterinary oversight
   - **Feed**: OTC to VFD
   - **Water**: Rx (specified in GFI #213)
Performance Indications (GFI #209)

• Phases out performance indications for certain antibiotics

**Therapeutic uses (still allowed)**

- **Disease treatment**
  Administration of an antimicrobial to an animal or group of animals that exhibit clinical disease

- **Disease control**
  Administration of an antimicrobial to an animal or group of animals in which morbidity or mortality has exceeded baselines

- **Disease prevention**
  Administration of an antimicrobial to an animal or group of animals that are considered to be at risk, but prior to onset of clinical disease

**Performance uses (prohibited)**

- **Growth, nutrition, health maintenance**
  Administration of an antimicrobial to an animal or group of animals that results in improved performance, e.g., weight gain or feed conversion
# Products Affected vs. Unaffected as Defined by FDA Guidance 152

<table>
<thead>
<tr>
<th>Unaffected</th>
<th>Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-Medically Important</strong></td>
<td><strong>Medically Important</strong></td>
</tr>
<tr>
<td>Products used exclusively in animals:</td>
<td>Products deemed “important for human medicine” &amp; used by both animals &amp; humans, such as:</td>
</tr>
<tr>
<td>- Ionophores (Rumensin®)</td>
<td>- Penicillins</td>
</tr>
<tr>
<td>- Polypeptides</td>
<td>- Cephalosporins</td>
</tr>
<tr>
<td>- Carbadox</td>
<td>- Quinolones</td>
</tr>
<tr>
<td>- Bambermycin</td>
<td>- Fluoroquinolones</td>
</tr>
<tr>
<td>- Pleuromutilin</td>
<td>- Tetracyclines</td>
</tr>
</tbody>
</table>

**Therapeutic uses** — still allowed under veterinary supervision
- Treat animals diagnosed with an illness
- Control the spread of illness in a herd
- Prevent illness in healthy animals when exposure is likely

**Production uses** — Still allowed
Enhance growth or improve feed efficiency

**Production uses** — No longer allowed
Enhance growth or improve feed efficiency
Antibiotics Affected (from GFI #152)

- “Medically important” for human use

<table>
<thead>
<tr>
<th>Antibiotics Affected</th>
<th>Affected</th>
<th>Blue = shared feed and/or water</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillins</td>
<td>Penicillin G, Penicillin V</td>
<td></td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>Tetracyclines, Oxytetracyclines, Chlortetracycline (CTC), Aureomycin®</td>
<td></td>
</tr>
<tr>
<td>Carbapenems</td>
<td>Sulfas, Sulmet, ASP, CSP 250</td>
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<tr>
<td>Monobactams</td>
<td>Pyrazinamide</td>
<td></td>
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<tr>
<td>Quinolones</td>
<td>Glycopeptides</td>
<td></td>
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<tr>
<td>Fluoroquinolones</td>
<td>Oxazolidinones</td>
<td></td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Streptogramins, Stafac®</td>
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<tr>
<td></td>
<td>Neomix®</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clindamycin, Lincomix®</td>
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<tr>
<td></td>
<td>Polymyxin B</td>
<td></td>
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<tr>
<td></td>
<td>Chloramphenicol</td>
<td></td>
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<tr>
<td></td>
<td>Metronidazole</td>
<td></td>
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<tr>
<td></td>
<td>Rifamycins</td>
<td></td>
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<tr>
<td></td>
<td>Isoniazid</td>
<td></td>
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<tr>
<td></td>
<td>Macrolides, Tylan® (tylosin), Pulmotil® (tilmicosin)</td>
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Implications

• Food producers aren’t losing all feed-grade antibiotics
• The way they’re used will change
• Key phrase is “medically important”
  – Refers to drugs important for therapeutic use in humans
Guidance for Industry #213

- The “how” component
- Recommendations for voluntarily aligning products with GFI #209
- Advises companies on how to revise:
  - Labeling
  - Promotion
- 2 options to change product labels
  - Voluntarily remove production indications
  - Seek new therapeutic indications at current doses
- Provides 3 years to comply (Dec. 2016)
21 CFR 558

• Proposes changes to VFD process
  – Strives toward less burdensome process
  – Provides greater flexibility for veterinarians to exercise professional training
  – Streamlines FDA administrative procedures
Veterinary Feed Directive (VFD)

• Existing regulatory framework for veterinary oversight of feed-use drugs (21 CFR 558)
• Designates VFDs as medicated feeds needing veterinary oversight
• Limits use of such products to veterinary oversight
• Requires a written statement (form) issued by a veterinarian
  – Authorizes manufacture & use of feed containing a drug
VFD Modernization

• Over a decade since introduction of VFDs
• Significant expansion of feed grade antibiotics requiring VFDs
• Streamlining current process is critical to facilitate transition of marketing status from OTC to VFD
• Goal: clarify requirements associated with veterinary authority & the use of VFD drugs
VFD Modernization

• GFI #209 assigns VFD status to more feed grade antibiotics

• This shift raised concerns around:
  – Limited experience with VFD process
  – Logistical & administrative burden
  – Access to veterinarians
  – Increased cost (producer, vet, feed mills)

• Draft for comment Dec. 2013

• Final rule June 3, 2015
  – Effective Oct. 1, 2015
VFD Modernization

• Because of those concerns, FDA modified VFD process

• Goals of modification
  – Improve the efficiency of the VFD program while continuing to protect public health (human & animal health)
  – Striving toward less burdensome process for all
  – Providing greater flexibility to veterinarians
  – Streamlining FDA administrative procedures
VFD Implementation Timing
Compliance Timeline

- FDA pursuing voluntary compliance
- FDA to evaluate progress 3 years after final publication
  - Guidance for Industry #213 finalized Dec. 2013
  - FDA will consider “further actions” as warranted

Q2, 2012: 209/213/VFD published
Q2, 2013: Public hearings
Q1, 2014: Sponsors must notify CVM of intent to engage
Q4, 2013: Release of final 213 & draft VFD
Q1, 2017: Implementation complete

June 3, 2015: Release of final VFD rule
Oct. 1, 2015: Final VFD rule goes into effect
Dec. 11, 2013: Release of final VFD rule
Compliance Timeline

• Voluntary approach:
  – Enables companies to efficiently make transitions
  – Provides time to understand policies
  – Enables companies to vary their own timelines
  – Acknowledges a significant undertaking by affected parties

• Approach **not voluntary** for producers or feed manufacturing once labels have been transitioned
Compliance Timeline

• 26 affected companies
• 100% have confirmed intent to engage with written response to FDA
Final VFD Rules

June 2015
VFD form requirements

• The veterinarian’s name, address and telephone number
• The client’s name, business or home address and telephone number
• The premises at which the animals specified in the VFD are located
• The date of VFD issuance
• The expiration date of the VFD
• The name of the VFD drug(s)
• The species and production class of animals to be fed the VFD feed
• The approximate number of animals to be fed the VFD feed by the expiration date of the VFD (no longer need to include total pounds of feed)
• The indication for which the VFD is issued
• The level of VFD drug in the feed and duration of use
• The withdrawal time, special instructions and cautionary statements necessary for use of the drug in conformance with the approval
• The number of reorders (refills) authorized, if permitted by the drug approval, conditional approval or index listing
• **The statement:** “Use of feed containing this veterinary feed directive (VFD) drug in a manner other than as directed on the labeling (extralabel use) is not permitted”
• An affirmation of intent for combination VFD drugs as described in 21 CFR 558.6(b)(6)
• The veterinarian’s electronic or written signature
VFD Recordkeeping Requirements

• Maintains record keeping requirement for VFDs for 2 years for veterinarian, client & distributor
  – Vet now maintains original VFD & sends copy to client & distributor

• Permits electronic storage of VFD records
  – If VFD is transmitted electronically, veterinarian no longer required to send hard copy to distributor

• All creation & storage of electronic forms needs to be 21 CFR 11 compliant

• Prohibits verbal issuance of VFD (e.g., by telephone)
VCPR Requirements

• Any veterinarian issuing a VFD be licensed to practice veterinary medicine and operate in compliance with appropriate State-defined veterinarian-client-patient relationship requirements

  - In States where the practice requirements do not require that a VFD be issued within the context of a State-defined VCPR, FDA is requiring that the VFD be issued within the context of a Federally-defined valid VCPR, as outlined in 21 CFR 530.3(i)

• VCPR requires that the veterinarian:

  1. Engage with the client to assume responsibility for making medical judgments about animal health and the need for medical treatment
  2. Have sufficient knowledge of the animal by virtue of examination and/or visits to the facility where animal is managed to initiate at least a general or preliminary diagnosis of the medical condition of the animal(s), and
  3. Provide for any necessary follow-up evaluation or care
VFD Product Classification

• Eliminates current automatic classification of VFD products to Category II
  – Access to Type A Concentration Category II products is restricted to licensed feed mills only
  – Change allows VFD products to be Category 1
    • Allows unlicensed feed manufacturers continued access to Type A medicated articles at concentrations currently used
  – As before, distributor must notify FDA before distributing VFD products for the first time

• Veterinarian is required to write the name of the VFD products on the VFD
  – The vet may choose to write the name of a pioneer or generic product name
  – The vet may choose to specify that a substitution of a product is not allowed; if the vet does not specify, the feed manufacturer may choose to use either
Combination Drugs

• Veterinarian must specify whether the VFD drug:
  – May be used in any approved combination in VFD feed
  – May be used in only specific approved combinations in VFD feeds
  – May not be used in any approved combination in VFD feed

• 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 VFD drug
Extra Label Use is Not Permitted

• “Use of feed containing this veterinary feed directive (VFD) drug in a manner other than as directed on the labeling (extra label use) is not permitted”
Expiration vs. Duration

- The **expiration** date defines the period of time for which the authorization to feed an animal feed containing a VFD drug is lawful
  
  - The expiration date on the VFD specifies the last day the VFD feed can be fed to the group of animals
  
  - The vet should use the expiration date that is specified in the label approval (e.g., 45 days for tilmicosin in beef cattle); where such date is not specified, the vet can write a date up to 6 months

- The **duration** determines the length of time the VFD feed is allowed to be fed to the animals, as specified on the product label (e.g., 14 days for tilmicosin in beef cattle)
Specifying Animals & Location

• The veterinarian should enter information about the location of the animals that would allow someone to locate the animals (e.g., address, GPS)
  – The vet may use his/her discretion to enter additional information (e.g., lot, site, pen) & should work with client to determine whether animals remain at the more specific location until the expiration date of the VFD
  – If a VFD is intended to authorize the use of a VFD feed in a group of animals that are located at more than one physical location, it is acceptable to include multiple specified locations for that group to be fed on the VFD feed by the expiration date on the VFD, provided 1) they can do so in compliance with professional licensing and 2) the feed is supplied by a single feed manufacturer/distributor
Defining Feed Distributors

• On-farm mixers that only manufacture medicated feeds for use in their own animals are not distributors

• On-farm mixers must only be manufacturing VFD feed for their use in their own animals on their own farm, meaning that the ownership of the feed mill, the animals and the animal production facility must be the same and the on-farm mixer must be the person using the VFD feed
  – If an on-farm mixer distributes to another producer, that mixer will be considered a distributor
Distribution Regulation

• Must only fill a VFD if the VFD contains all required information

• One-time notifications
  – **Notice To FDA of Distribution of VFD Feeds** to FDA that you intend to handle/distribute VFD drug-containing medicated feeds
  – **Acknowledgement of Distribution Limitations for VFD Feeds** document stating that the purchasers will sell the VFD feeds only to producers with valid VFD orders or to other distributors for whom they have acknowledgement notices
Notice To FDA of Distribution of VFD Feeds

I/we hereby notify the Food and Drug Administration that I/we have begun distributing VFD feeds.

________________________________________
Signature

________________________________________
Name of firm or individual

________________________________________
Business Address

________________________________________
Date

This notice should be sent to:
Center for Veterinary Medicine (HFV-226)
7500 Standish Place
Rockville, MD 20855

Acknowledgment of Distribution for VFD Feeds

I/we hereby acknowledge that, as required by federal law, I/we shall distribute VFD feeds received by me/us from:

________________________________________
(Name and address of shipper)

As follows:

1. To an animal production facility, if the owner or operator of that facility provides me/us with a copy of a veterinary feed directive covering the quantity of feed involved and the animal production facility to which the feed is being distributed; or

2. To another person for further distribution, if that person provides me/us with a written acknowledgment similar to this acknowledgment.

________________________________________
Signature

________________________________________
Name of firm or individual

________________________________________
Street Address

________________________________________
Date

3. By signing this Acknowledgment of Distribution I/we affirm that I/we have notified FDA of our intent to distribute VFD medications.
FDA Enforcement Strategy

• FDA first intends to provide education and training for stakeholders subject to this final rule such as veterinarians, clients (animal producers), feed mill distributors and other distributors

• FDA will then engage in risk-based general surveillance, as well as for-cause inspection assignments
  
  – FDA intends to use information such as history of VFD use and the volume of VFD feed being produced to focus inspectional resources within the industry based on risk
  
  – FDA anticipates that it will utilize various sources for obtaining such information including FDA food and drug registration information, feed mill licensing information, the VFD distributor notifications FDA receives, and VFD distribution records maintained by drug sponsors
Implementing a VFD (Cattle)
Current Pulmotil Cattle VFD Form

Pulmotil® (illicitosin) Veterinary Feed Directive for use in Cattle

Client: ____________________________  Veterinarian: ____________________________

Address: ____________________________  Address: ____________________________

Phone #: ____________________________  Phone #: ____________________________

Fax #: ____________________________  Fax #: ____________________________

Cattle to be treated (number and location): ____________________________

Special Instructions: ____________________________

Mix into Type C Meclofenacet Feed to Provide:

<table>
<thead>
<tr>
<th>Type C Meclofenacet Feed</th>
<th>Amount of Type C Meclofenacet Feed</th>
<th>Resulting concentration of Pulmotil</th>
<th>Amount of Feed to be Mixed</th>
<th>Resulting concentration of Pulmotil</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 lbs</td>
<td>10 lbs</td>
<td>0.01%</td>
<td>90 lbs</td>
<td>0.01%</td>
</tr>
<tr>
<td>100 lbs</td>
<td>20 lbs</td>
<td>0.02%</td>
<td>80 lbs</td>
<td>0.02%</td>
</tr>
</tbody>
</table>

VFD Expiration Date: Month/Day/Year (not to exceed 45 days)

VFD Form Expected to Change in Late 2015.

*VFD form expected to change in late 2015.
Also to be included:
- Indication
- Withdrawal time, special instructions & cautionary statements

Pulmotil® (tilmicosin) Veterinary Feed Directive for use in Cattle

Client: ___________________________  Veterinarian: ___________________________
Address: ___________________________  Address: ___________________________

Phone #: ___________________________  Phone #: ___________________________
Fax #: ___________________________  Fax #: ___________________________

Cattle to be treated (number and location):

Will require approx. # of animals

Mix into Type C Medicated Feed to Provide:

<table>
<thead>
<tr>
<th>Drug (Ingredient)</th>
<th>Drug Level or Any Special Instructions</th>
<th>Initial</th>
</tr>
</thead>
</table>

No longer requires calculation of lbs of feed; will require approx. # of animals

No longer requires license # & state
Caution Statement

• Each product approved under the VFD regulations includes the following caution:

Caution: Federal law restricts medicated feed containing this veterinary feed directive (VFD) drug to use by or on the order of a licensed veterinarian.
Distribution of VFD form

- Original form must be stored by veterinarian

| White Copy — Veterinarian | Canary Copy — Client | Pink Copy — Supplier |

Note: color-coded forms are Elanco-only forms.
Implementing a VFD (Swine)
*VFD form expected to change in late 2015.*
Pulmotil® (tilmicosin) Swine Veterinary Feed Directive

Also to be included:
- Name of VFD drug
- Indication
- Level of VFD drug in feed & duration
- Withdrawal time, special instructions & cautionary statements
- Affirmation of intent for combination drugs

Expiry date length dependent on product label

Mix into Type C medicated feed to provide:
- total lbs. Type C feed at 181 g/ton
- total lbs. Type C feed at 272 g/ton
- total lbs. Type C feed at 363 g/ton

No longer requires calculation of lbs of feed; will require approx. # of animals

No longer requires license # & state

Expiration date length dependent on product label

Also to be included:
- Name of VFD drug
- Indication
- Level of VFD drug in feed & duration
- Withdrawal time, special instructions & cautionary statements
- Affirmation of intent for combination drugs
Caution Statement

• Each product approved under the VFD regulations includes the following caution:

Caution: Federal law restricts medicated feed containing this veterinary feed directive (VFD) drug to use by or on the order of a licensed veterinarian.
Distribution of VFD form

- Original form must be stored by veterinarian

White Copy — Veterinarian
Canary Copy — Client
Pink Copy — Supplier

Note: color-coded forms are Elanco-only forms.
Electronic VFDs
FeedLINK Features – eVFD

• Ease the burden of paperwork
  – Spend less time creating VFDs and reduce manual inaccuracies by creating electronic VFD prescriptions

• Provide a reliable source of documentation
  – Maintain VFD compliance easily with a secure, web-based software solution
  – FeedLINK retains veterinarians’ eVFDs for the required two-year period

• Enhance communication with stakeholders
  – Automatically send VFDs to feed suppliers and producers upon creation
  – Renew VFD orders in seconds with an email notification linking to the pre-populated VFD

• 21 CFR Part 11 Compliant
Visit globalvetlink.com to get started
• Click “Login/Sign Up” in the top-right corner to create a new account or to sign in
Click “eVFD”, and then provide your business name and other pertinent business information.
To create an eVFD, first either ‘find by name’ a previous producer who you intend to create an eVFD for or click the “+” to create a new contact.

Always use the TAB button on your keyboard to navigate the site; pressing ENTER will attempt to submit an incomplete eVFD.
Contact GlobalVetLINK

• Sales team: (515) 817-5703
  – For training and sales support with new clients

• Technical support: (515) 817-5704
  – To set up accounts, add feed suppliers, or other technical system support

• Monday-Friday, 8 a.m.-5 p.m. (CST)

www.globalvetlink.com
Impact on Elanco
Impact on Elanco

• Elanco publicly supports FDA initiatives:
  – Aligns with Elanco global antibiotic policy
  – Expedites VFD modernization
  – Protects long-term access
  – Helps support public health

• Elanco will support initiatives via:
  – Resources
  – Leadership
  – Commitment
Impact on Elanco

• In USA, Tylan® premix & Hygromix® use:
  – Will be under the VFD process/require veterinarian oversight

• Hygromix:
  – Moves to VFD status but claims would remain

• Tylan Soluble (tylosin tartrate):
  – Moved to a prescription status
Impact on Elanco

• Tylan® premix for **swine**
  – Claims for weight gain & feed efficiency withdrawn
  – Claims for swine dysentery & ileitis remain (requires VFD)

• Tylan premix for **cattle**
  – Claim for reduction of liver abscesses remains (requires VFD)
Impact on Elanco

• Pulmotil (tilmicosin)
  – Continues to be a VFD product
Impact on Elanco

• Ionophores remain unaffected
# Elanco’s 8-Point Antibiotic Stewardship Plan

<table>
<thead>
<tr>
<th>1. Act with responsibility globally</th>
</tr>
</thead>
<tbody>
<tr>
<td>Act with responsibility globally—not just according to U.S. regulation—by working with food producers and retailers to provide training and encourage policies that reduce shared-class antibiotic use and increase veterinarian oversight.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Cease marketing of growth promotion</th>
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<tbody>
<tr>
<td>Cease marketing of growth promotion uses for shared-class antibiotics and complete full regulatory change to end growth promotion use of shared-class antibiotics globally by the end of 2016.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. Eliminate continuous antibiotic use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Help customers eliminate continuous use of shared-class antibiotics for therapy purposes by providing an alternative.</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>4. Eliminate over-the-counter sales</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eliminate over-the-counter sales of shared-class antibiotics globally—including injectable products—where veterinarian oversight exists.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. Eliminate concurrent use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eliminate concurrent use of shared-class antibiotics to treat the same disease.</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>6. Support veterinary oversight</th>
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<tbody>
<tr>
<td>Support veterinary oversight and responsible use, including helping build infrastructure globally.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7. Develop new animal-only antibiotics</th>
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<tbody>
<tr>
<td>Develop new animal-only antibiotics. No animal should ever be treated with a shared-class antibiotic if an animal-only option exists. Animal-only antibiotics optimize animal welfare without compromising human use antibiotics.</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>8. Create alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elanco commits to invest two-thirds of our food animal research budget to quickly evaluate 25 candidates and deliver 10 viable non-antibiotic development projects that address diseases where there are few, or no, alternatives to shared-class antibiotics. (Respiratory disease and enteric disease in cattle, swine and poultry and mastitis in cattle.)</td>
</tr>
</tbody>
</table>
Background

• Antibiotic resistance is a complex issue and the solutions to addressing it are equally complex.

• In 2013, Elanco announced it’s Antibiotic Policy, which outlines our global approach to the responsible use of antibiotics and to help preserve effectiveness of antibiotics for human and animal health.

• Since 2013, Elanco has been leading efforts, including shaping public policy for the responsible use of antibiotics in partnership with stakeholders across the globe.

• Elanco’s 8-Point Antibiotic Stewardship Plan aligns with our Global Antibiotic Policy and further outlines our commitment to this issue.
Elanco’s Position

• For medically important antimicrobials, Elanco supports:
  – The responsible use for therapeutic purposes with veterinarian oversight
  – Voluntarily narrowing use to therapeutic uses only
  – No longer promoting use for performance purposes
  – Transitioning label indications to therapeutic uses only
Elanco’s Position

• Invest in innovation

Pursue advances & treatments that lessen reliance on antibiotics

Seek new therapeutic indications for treatment, control & prevention of diseases

Support use of antimicrobials used only in animals for growth & performance (where permitted)

Provide services that help verify & validate responsible product use
<table>
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<tr>
<th>Subject</th>
<th>Policy highlights</th>
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<td><strong>Internal governance</strong></td>
<td>Provide oversight by global antimicrobials team</td>
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<td><strong>Product registrations</strong></td>
<td>Seek therapeutic indications for all antimicrobial classes</td>
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<td></td>
<td>Support use of animal-only products for growth/performance</td>
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<td><strong>New product development</strong></td>
<td>Support existing products</td>
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<td>Pursue appropriate extended uses</td>
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<td>Seek new platforms for animal care</td>
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<td><strong>Professional oversight</strong></td>
<td>Support oversight of antibiotic use by veterinarians</td>
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<td><strong>Risk-based assessment</strong></td>
<td>Review products, resistance monitoring, data, research, etc., to protect human &amp; animal health</td>
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<td><strong>Partnerships</strong></td>
<td>Collaborate with industry groups &amp; leaders</td>
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How to use Tylan® premix for swine

<table>
<thead>
<tr>
<th>For ileitis control:</th>
<th>Recommendation:</th>
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<tr>
<td>Feed Tylan at 100 g/ton for at least 3 weeks, followed by 40 g/ton to market weight.</td>
<td>Begin feeding Tylan at 12-15 weeks of age or 3 weeks prior to seroconversion,(^1,2) because gross or microscopic lesions appear well in advance of seroconversion/disease.</td>
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* No withdrawal required when fed according to label directions.

How to use Tylan® premix for poultry

- For increased rate of weight gain and improved feed efficiency in broilers (indication to be withdrawn), feed Tylan at
  - Tylan 40 per ton of Type C Feed: 0.1 to 1.25 lbs.
  - Tylosin per ton of Type C Feed: 4 to 50 g
- Feed continuously as the sole ration
- To aid in the control of chronic respiratory disease associated with *Mycoplasma gallisepticum* in broilers
  - Tylan 40 per ton of Type C Feed: 20 to 25 lbs.
  - Tylosin per ton of Type C Feed: 800 to 1,000 g*
- To aid in the control of chronic respiratory disease associated with *Mycoplasma gallisepticum* in replacement chickens
  - 1,000 g/ton
- Tylan requires a 5-day withdrawal period before slaughter when fed at 800 to 1,000 g/ton.

* No withdrawal required when fed according to label directions.

How to use Tylan® Premix for beef cattle

- For reduction of incidence of liver abscesses associated with *Fusobacterium necrophorum* and *Arcanobacterium pyogenes*:
  - Feed tylosin continuously at 8-10 g/ton (90% DM) to deliver 60-90 mg/hd/d.

Hygromix® directions for use

- For use as an aid in the control of parasite infections in chickens associated with *Ascaris galli, Heterakis gallinae* and *Capillaria obsignata*.
- Mix 1.0-1.5 lbs. Hygromix 8 per ton of Type C medicated feed for 8-12 g of hygromycin B per ton.
- Feeds containing Hygromix must be withdrawn 3 days prior to slaughter.

The labels contain complete use information, including cautions and warnings.
Always read, understand and follow the label and use directions.
### Pulmotil® directions for use for cattle

- **Feeds containing tilmicosin must be withdrawn 28 days prior to slaughter.**
- **CAUTION:** Federal law limits this drug to use under the professional supervision of a licensed veterinarian. Animal feed bearing or containing this veterinary feed directive drug shall be fed to animals only by or upon a lawful veterinary feed directive issued by a licensed veterinarian in the course of the veterinarian's professional practice.
- **For the control of Bovine Respiratory Disease (BRD) in groups of beef and non-lactating dairy cattle, where active BRD has been diagnosed in at least 10% of the animals in the group:** Feed continuously for a single, 14-day period at 568 to 757 g/ton of tilmicosin (100% DM basis) in a Type C medicated feed as the sole ration to provide 12.5 mg/kg of body weight/hd/d.

### Pulmotil® directions for use for swine

- **Feeds containing tilmicosin must be withdrawn 7 days prior to slaughter.**
- **CAUTION:** Federal law limits this drug to use under the professional supervision of a licensed veterinarian. Animal feed bearing or containing this veterinary feed directive drug shall be fed to animals only by or upon a lawful veterinary feed directive issued by a licensed veterinarian in the course of the veterinarian's professional practice.
- **For the control of swine respiratory disease associated with *Actinobacillus pleuropneumoniae* and *Pasteurella multocida,** feed continuously at 181–363 g/ton for a 21-day period, beginning approximately 7 days before an anticipated outbreak.
Tylosin Tartrate

Equivalent to 100 g (3.53 oz) tylosin base

CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

For oral use in chickens, turkeys, swine, and honey bees.

Macrolide Antimicrobial, NADA 13-076, approved by FDA

Indications

Chickens: For the control of mortality caused by Mycoplasma gallisepticum in broiler chickens. As an aid in the treatment of chronic respiratory disease (CRD) associated with Mycoplasma gallisepticum in broiler and replacement chickens. For the control of CRD associated with Mycoplasma synoviae in turkey poults.

Turkeys: For the reduction in severity of effects of infectious disease associated with Mycoplasma synoviae.

Swine: For the treatment and control of swine dysentery (SD) associated with Brachyspira hyodysenteriae. For the treatment and control of SD associated with Brachyspira hyodysenteriae when followed immediately by Tylosin Type A medicated article in feed.

For the control of porcine proliferative enteropathy (PPE) caused by Lactobacillus undercarinatus when followed immediately by Tylosin Type A medicated article in feed.

Honey Bees: For the control of American Foulbrood (Bacillus licheniformis). Ingredients Tylosin Tartrate

Dosage and Administration

Dosage:

Chickens: NE indication: 851 to 1,419 mg/gallon (226 to 375 ppm) in drinking water.

CRD indications: 2,000 mg/gallon (520 ppm) in drinking water.

Turkeys: 2,000 mg/gallon (520 ppm) in drinking water.

Swine: 250 mg/gallon (66 ppm) in drinking water.

Honey Bees: 200 mg/gallon in concentrations/powdered sugar.

Mixing Directions for Medicated Drinking Water:

Always add the water to the powder. Do not pour the powder into the water. Prepare a fresh Tylosin Solubilizer solution every three days. When mixing and handling tylosin, use protective clothing and impervious gloves. If using a water medicating pump, use a separate pump, otherwise mix as follows:

For animals of 100 kg (220 lbs) or less, mix 1 gallon of water (3785 ml) the powder to make a concentrated solution. To make medicated drinking containing 250 mg/gallon (66 ppm) mix this concentrated solution with water to make 400 gallons (1514 liters) of medicated drinking water. To make medicated drinking containing 1,419 mg/gallon (375 ppm) mix this concentration with water to make 117 gallons (444 liters) of medicated drinking water.

Mixing Directions for Water Medicating Pump (1% inclusion):

<table>
<thead>
<tr>
<th>Desired Concentration in Drinking water</th>
<th>Jars of Tylosin Soluble</th>
<th>Volume of Water to Make Stock Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>250 mg/gallon (66 ppm)</td>
<td>1</td>
<td>3 gallons + 13 ounces</td>
</tr>
<tr>
<td>851 mg/gallon (225 ppm)</td>
<td>5</td>
<td>4 gallons + 77 ounces</td>
</tr>
<tr>
<td>1,419 mg/gallon (375 ppm)</td>
<td>9</td>
<td>5 gallons + 4 ounces</td>
</tr>
<tr>
<td>2,000 mg/gallon (528 ppm)</td>
<td>10</td>
<td>3 gallons + 115 ounces</td>
</tr>
</tbody>
</table>

*This table applies only if the water medicating pump is set to deliver 1 ounce of stock solution per gallon of drinking water.

Mixing Directions for Use in Honey Bees: Mix 208 mg tylosin in 20 g powdered sugar. Use immediately.

Directives for Use

Chickens: NE indication: Administer medicated drinking water for a single day period in broiler chickens. To ensure all birds receive the intended medication, only medicated water should be available. These practices should be followed to ensure both food safety and responsible antimicrobial drug use in chickens. 1) Use in flocks exhibiting signs of a nervous disease outbreak, for example, increased mortality and lesions characteristic of salicylic disease, to prevent recurrence; 2) Administer the full dose and dose regimen once medication is initiated; 3) Use of Tylosin Soluble or another macrolide is not advised if additional therapy is needed beyond the original course of medication. CRD Indications: Administer medicated drinking water for three days; however, medicated water should be administered for one to five days depending upon severity of infection. Treated chickens must consume enough medicated water to provide 50 mg per pound of body weight per day. Only medicated water should be available to the birds.

Turkeys: Administer medicated drinking water for three days; however, medicated water may be administered for two to five days depending upon severity of infection. Treated turkeys must consume enough medicated water to provide 60 mg per pound of body weight per day. Only medicated water should be available to the birds.

Swine: SD Indications: Administer medicated drinking water for 3 to 10 days depending upon severity of infection. Alternatively, medicated drinking water for 3 to 10 days, followed by 40 to 100 g/ton of complete feed Type C medicated feed manufactured from Tylosin Type A medicated articles for 2 to 6 weeks. Only medicated water should be available to swine while medicating with Tylosin Soluble. PPE Indication: Administer medicated drinking water for 3 to 10 days, followed by 40 to 100 g/ton of complete feed Type C medicated feed manufactured from Tylosin Type A medicated articles for 2 to 6 weeks. Only medicated water should be available to swine while medicating with Tylosin Soluble.

Honey Bee Gallons: Administer three treatments of medicated concentrations on one day in 100 gallons of water.

User Safety Warnings: Not for Human Use. Keep out of reach of children. Avoid contact with human skin. Exposure to tylosin may cause a rash.

Residue Warnings: Chickens: Must not be slaughtered for food within 24 hours after treatment. Do not use in layers producing eggs for human consumption.

Turkeys: Must not be slaughtered for food within five days after treatment.

Swine: Must not be slaughtered for food within 48 hours after treatment.

Honey bees: The bees should not be fed on the day of treatment. Do not use in layers producing eggs for human consumption.

Manufactured for:

Elanco Animal Health

A Division of Eli Lilly and Company

Indianapolis, IN 46225, USA

Product of the United Kingdom

Avoid Moisture

Restricted Drug (California) – Use Only as Directed.

To report suspected adverse events, for technical assistance, or to obtain a Material Safety Data Sheet (MSDS), call 1-800-426-3441.

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