Medically Important Antimicrobials in Animal Agriculture

Sheep

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Veterinary Medical Officer
Office of the Director
Center for Veterinary Medicine
FDA
Outline

• Take Home

• Changes to Affected Products
  – Changes to Oral Dosage Form Products
  – Changes to Medicated Feed Products

• Sources of Information

• Take Home
Take Home

All drug sponsors have aligned all affected applications with the GFI # 213 recommendations by the January 2017 target date.
Outline

• Take Home

• **Changes to Affected Products**
  – Changes to Oral Dosage Form Products
  – Changes to Medicated Feed Products
    • Major & Minor Species

• Sources of Information

• Take Home
Changes to Affected Products

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

84 were completely withdrawn

Of the remaining 208 applications,

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

Production (e.g., growth promotion) indications associated with medically important antimicrobials were withdrawn from all applications that included such indications for use.
Outline

• Take Home
• Changes to Affected Products
  Changes to Oral Dosage Form Products
  Changes to Medicated Feed products
    • Major & Minor Species
• Sources of Information
• Take Home
Changes to Affected Products

- 21 CFR Part 520
  Medically Important Antimicrobials regulated by CVM/FDA as oral dosage form new animal drugs.

93 Applications Transitioned from OTC to Rx Marketing Status.

In reporting year 2015, these applications accounted for ~21% of the sales of all medically important antimicrobials.
21 CFR Part 520
OTC to Rx

• Oral Dosage Form New Animal Drugs
  • (21 CFR Part 520)

• Label – Limitation

• Federal Law restricts this drug to use by or on the order of a licensed veterinarian.
Changes to Affected Products

• Rx – Examples
  • 21 CFR Part 520.1660d

• Oxytetracycline Hydrochloride
  – N 008-622
  – A 200-026
  – A 200-146
  • Species: Sheep (Domestic)
  • Class: No Use Class Stated or Implied
  • Indication: Control and treatment of bacterial enteritis caused by \textit{E. coli} and bacterial pneumonia (shipping fever complex) caused by \textit{P. multocida} susceptible to oxytetracycline.
Changes to Affected Products

- Rx – Examples
- 21 CFR Part 520.1484

- Neomycin – (Sheep & Goats)
  - A 200-113
  - A 200-130
  - A 200-235
  - Species: Sheep (Domestic)
  - Class: No Use Class Stated or Implied
  - Indication: For the treatment and control of colibacillosis (bacterial enteritis) caused by *Escherichia coli* susceptible to neomycin.
## Changes to Affected Products

**Affected Oral Dosage Form 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, Sulfadinoxaline</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Chlortetracycline, Oxytetracycline, Tetracycline</td>
</tr>
</tbody>
</table>
Changes to Affected Products

• 21 CFR Part 520
  • ELU

• The Animal Medicinal Drug Use Clarification Act (AMDUCA) of 1994 and the regulations published at 21 CFR part 530 describe the requirements for, and restrictions on, extra-label drug use.
Changes to Affected Products

- 21 CFR Part 520
  - Rx – VCPR

- On – label: State VCPR
- Off-label: Federal VCPR (21 CFR Sec.530.3(i))

See: [http://www.ecfr.gov/cgi-bin/text-idx?SID=5ad83a5a41b724e95d9669f83c6475df&mc=true&node=pt21.6.530&rgn=div5](http://www.ecfr.gov/cgi-bin/text-idx?SID=5ad83a5a41b724e95d9669f83c6475df&mc=true&node=pt21.6.530&rgn=div5)
Outline

• Take Home
• Changes to Affected Products
  Changes to Oral Dosage Form Products
  Changes to Medicated Feed Products
    • Major & Minor Species
• Sources of Information
• Take Home
Changes to Affected Products

• 21 CFR Part 558
Medically Important Antimicrobials regulated by CVM/FDA as New Animal Drugs for use in Animal Feed.

115 Applications Transitioned from OTC to VFD Marketing Status.

In reporting year 2015, these applications accounted for ~74% of sales of all medically important antimicrobials.
21 CFR Part 558
OTC to VFD

• VFD Medicated Feed
  • (21 CFR Part 558)

• Label – Special Considerations

• Federal Law restricts medicated feed containing this veterinary feed directive (VFD) drug to use by or on the order of a licensed veterinarian.
# Voluntary Changes of Affected Products

## New Animal Drugs for use in Animal Feed

<table>
<thead>
<tr>
<th>Antimicrobial Class</th>
<th>Specific drugs approved for use in feed</th>
</tr>
</thead>
<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>
Extralabel Use

• ELU Prohibited - animal feed

• Limitations of Extralabel use

• ...

• (b) Extralabel use of an approved new animal drug or human drug in or on an animal feed; 21 CFR Sec. 530.11
Extralabel Use
CPG 615.115

• Policy Statement

• Considerations
  – General
  – Veterinarian
  – Producer
  – Distributor/Manufacturer
Changes to Affected Products
21 CFR Part 558

- Major vs Minor Species

The term `major species' means cattle, horses, swine, chickens, turkeys, dogs, and cats, ... 21 U.S.C. 321 (nn)

The term `minor species' means animals other than humans that are not major species. 21 U.S.C. 321 (oo)
Extralabel Use
CPG 615.115

• Policy Statement
• Considerations
Extralabel Use
CPG 615.115

• Policy Statement
  – ELU
  – AMDUCA
  – However
Extralabel Use
CPG 615.115

**Policy Statement –**

- However, when

1. there are no approved treatment options available and
2. the health of animals is threatened, and
3. suffering or death would result from failure to treat the affected animals,

extra label use of medicated feed may be **considered** for treatment of **minor species**.
Extralabel Use
CPG 615.115

• Policy Statement –

• … no approved treatment options available …
  (OTC or VFD options considered)

  – Goats

  – Sheep
# Goats

## OTC - examples

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Proprietary Name</th>
<th>NADA/ANADA</th>
<th>Label Type</th>
<th>Indications</th>
<th>Marketing Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decoquinate (liquid)</td>
<td>DECCOX</td>
<td>N039-417</td>
<td>Type B</td>
<td>For the prevention of coccidiosis in young goats caused by Eimeria christenseni and E. ninakohlyakimovae.</td>
<td>OTC</td>
</tr>
<tr>
<td>Decoquinate</td>
<td>DECCOX</td>
<td>N039-417</td>
<td>Type C</td>
<td>For the prevention of coccidiosis in young goats caused by Eimeria christenseni and E. ninakohlyakimovae.</td>
<td>OTC</td>
</tr>
<tr>
<td>Decoquinate</td>
<td>DECCOX</td>
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<td>For the prevention of coccidiosis in young goats caused by Eimeria christenseni and E. ninakohlyakimovae.</td>
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</tbody>
</table>
## Goats

### OTC - examples

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<th>Active Ingredient</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Monensin</td>
<td>RUMENSIN</td>
<td>N095-735</td>
<td>Type C</td>
<td>For the prevention of coccidiosis caused by Eimeria crandallis, E. christenseni, and E. ninakohlyakimovae in goats maintained in confinement.</td>
<td>OTC</td>
</tr>
<tr>
<td>Morantel tartrate</td>
<td>RUMATEL</td>
<td>N092-444</td>
<td>Type C</td>
<td>For the removal and control of mature gastrointestinal nematode infections of goats including Haemonchus contortus, Ostertagia (Teladorsagia) circumcincta, and Trichostrongylus axei.</td>
<td>OTC</td>
</tr>
</tbody>
</table>
Goats/kids – excluding lactating goats/dairy females 12 months of age or older

**VFD - examples**

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Proprietary Name</th>
<th>NADA/ANADA</th>
<th>Label Type</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neomycin Sulfate</td>
<td>NEOMIX</td>
<td>N140-976</td>
<td>Type C</td>
<td>For the treatment and control of colibacillosis (bacterial enteritis) caused by <em>Escherichia coli</em> susceptible to neomycin.</td>
</tr>
</tbody>
</table>
Extralabel Use
CPG 615.115

• **Policy Statement** –

• … no approved treatment options available …
  –Goats
  –Sheep
Sheep

• **Production Classes**

• Breeding Sheep
• Growing Sheep
• Sheep (Multiple classes)

(See the link to GFI # 191 in sources of information below for more on production classes.)
# Breeding Sheep

## VFD - examples

<table>
<thead>
<tr>
<th>Active Ingredient</th>
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<th>Label Type</th>
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<th>Marketing Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlortetracycline</td>
<td>CHLORMAX</td>
<td>N046-699</td>
<td>Type C</td>
<td>For reducing the incidence of (vibronic) abortion caused by Campylobacter fetus infection susceptible to chlortetracycline.</td>
<td>VFD (Effective 1/1/17)</td>
</tr>
<tr>
<td>Chlortetracycline</td>
<td>AUREOMYCIN</td>
<td>N048-761</td>
<td>Type C</td>
<td>For reducing the incidence of (vibronic) abortions caused by Campylobacter fetus infection susceptible to chlortetracycline in breeding sheep.</td>
<td>VFD (Effective 1/1/17)</td>
</tr>
<tr>
<td>Chlortetracycline</td>
<td>CLTC</td>
<td>N092-286</td>
<td>Type C</td>
<td>For reducing the incidence of (vibronic) abortions caused by Campylobacter fetus infection susceptible to chlortetracycline in breeding sheep.</td>
<td>VFD (Effective 1/1/17)</td>
</tr>
<tr>
<td>Chlortetracycline</td>
<td>PENNCHLOR</td>
<td>N138-935</td>
<td>Type C</td>
<td>For reducing the incidence of (vibronic) abortions caused by Campylobacter fetus infection susceptible to chlortetracycline in breeding sheep.</td>
<td>VFD (Effective 1/1/17)</td>
</tr>
<tr>
<td>Chlortetracycline</td>
<td>DERACIN</td>
<td>A200-510</td>
<td>Type C</td>
<td>For reduction in the incidence of (vibronic) abortions caused by <em>Campylobacter fetus</em> infection susceptible to chlortetracycline in breeding sheep.</td>
<td>VFD (Effective 1/1/17)</td>
</tr>
</tbody>
</table>
# Sheep (Multiple Classes)

## OTC - examples

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<thead>
<tr>
<th>Active Ingredient</th>
<th>Proprietary Name</th>
<th>NADA/ANADA</th>
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<th>Marketing Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decoquinate</td>
<td>DECCOX</td>
<td>N039-417</td>
<td>Type C</td>
<td>For the prevention of coccidiosis in young sheep caused by <em>Eimeria ovinoidalis</em>, <em>E. parva</em>, <em>E. bakuensis</em>, and <em>E. crandallis</em>.</td>
<td>OTC</td>
</tr>
<tr>
<td>Decoquinate</td>
<td>DECCOX</td>
<td>N039-417</td>
<td>Type C</td>
<td>For the prevention of coccidiosis in young sheep caused by <em>Eimeria ovinoidalis</em>, <em>E. parva</em>, <em>E. bakuensis</em>, and <em>E. crandallis</em>.</td>
<td>OTC</td>
</tr>
<tr>
<td>Decoquinate</td>
<td>DECCOX</td>
<td>N039-417</td>
<td>Type C</td>
<td>For the prevention of coccidiosis in young sheep caused by <em>Eimeria ovinoidalis</em>, <em>E. parva</em>, <em>E. bakuensis</em>, and <em>E. crandallis</em>.</td>
<td>OTC</td>
</tr>
<tr>
<td>Decoquinate (liquid)</td>
<td>DECCOX</td>
<td>N039-417</td>
<td>Type B</td>
<td>For the prevention of coccidiosis in young sheep caused by <em>Eimeria ovinoidalis</em>, <em>E. parva</em>, <em>E. bakuensis</em>, and <em>E. crandallis</em>.</td>
<td>OTC</td>
</tr>
</tbody>
</table>
Sheep (Multiple Classes)
VFD - examples

<table>
<thead>
<tr>
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<tr>
<td><strong>Neomycin Sulfate</strong></td>
<td>NEOMIX</td>
<td>N140-976</td>
<td>Type C</td>
<td>For the treatment and control of colibacillosis (bacterial enteritis) caused by <em>Escherichia coli</em> susceptible to neomycin.</td>
</tr>
</tbody>
</table>
# Sheep (Multiple Classes)

## VFD - examples

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Proprietary Name</th>
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<th>Label Type</th>
<th>Indications</th>
<th>Marketing Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neomycin Sulfate and Oxytetracycline</td>
<td>NEO-TERRAMYCIN</td>
<td>N094-975</td>
<td>Type C</td>
<td>Treatment of bacterial enteritis caused by <em>Escherichia coli</em> and bacterial pneumonia caused by <em>Pasteurella multocida</em> susceptible to oxytetracycline; treatment and control of colibacillosis (bacterial enteritis) caused by <em>E. coli</em> susceptible to neomycin</td>
<td>VFD (Effective 1/1/17)</td>
</tr>
<tr>
<td>Neomycin Sulfate and Oxytetracycline</td>
<td>NEO-OXTC</td>
<td>N138-939</td>
<td>Type C</td>
<td>Treatment of bacterial enteritis caused by <em>Escherichia coli</em> and bacterial pneumonia caused by <em>Pasteurella multocida</em> susceptible to oxytetracycline; treatment and control of colibacillosis (bacterial enteritis) caused by <em>E. coli</em> susceptible to neomycin</td>
<td>VFD (Effective 1/1/17)</td>
</tr>
</tbody>
</table>
## Sheep (Multiple Classes)

### VFD - examples

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Proprietary Name</th>
<th>NADA/ANADA</th>
<th>Label Type</th>
<th>Indications</th>
<th>Marketing Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oxytetracycline</strong></td>
<td>TERRAMYCIN</td>
<td>N008-804</td>
<td>Type C</td>
<td>For treatment of bacterial enteritis caused by <em>Escherichia coli</em> and bacterial pneumonia caused by <em>Pasteurella multocida</em> susceptible to oxytetracycline.</td>
<td>VFD (Effective 1/1/17)</td>
</tr>
<tr>
<td><strong>Oxytetracycline</strong></td>
<td>OXTC</td>
<td>N095-143</td>
<td>Type C</td>
<td>For sheep for treatment of bacterial enteritis caused by <em>Escherichia coli</em> and bacterial pneumonia caused by <em>Pasteurella multocida</em> susceptible to oxytetracycline.</td>
<td>VFD (Effective 1/1/17)</td>
</tr>
<tr>
<td><strong>Oxytetracycline</strong></td>
<td>OTC</td>
<td>N138-938</td>
<td>Type C</td>
<td>For treatment of bacterial enteritis caused by <em>Escherichia coli</em> and bacterial pneumonia caused by <em>Pasteurella multocida</em> susceptible to oxytetracycline.</td>
<td>VFD (Effective 1/1/17)</td>
</tr>
</tbody>
</table>
Extralabel Use
CPG 615.115

• Policy Statement
• Considerations
Extralabel Use
CPG 615.115

• Policy Statement

• Considerations
  – General
  – Veterinarian
  – Producer
  – Distributor/Manufacturer
Extralabel Use
CPG 615.115

• **Considerations**
  – General - 7
    • Prior written recommendation/VCPR
    • Minor species & indications not on labeling/withdrawal time.
    • Approved Type A medicated article
    • Similar minor species – *mammal = mammal*
    • Not appropriate for unconfined wildlife
    • Animal health/suffering or death
    • Not promoted or advertised
Extralabel Use
CPG 615.115

• Policy Statement

• Considerations
  – General
  – Veterinarian
  – Producer
  – Distributor/Manufacturer
Extralabel Use
CPG 615.115

• Considerations
  – Veterinarian
    • General
    • OTC Medicated Feed
    • VFD Medicated Feed
Extralabel Use
CPG 615.115

• **Considerations**
  – Veterinarian

• **General**
  – All previous General Considerations, plus
  – Make a careful diagnosis and therapeutic indication
  – No therapeutic dosage form that can be used practically under legal ELU
  – Ensure Identity of treated animals
  – Establish a withdrawal period
  – No unsafe drug residues
  – Report adverse drug reactions
Extralabel Use
CPG 615.115

• C. Veterinary Considerations
  • General considerations

• Made a determination within the context of a valid veterinarian-client-patient relationship that there is no approved new animal drug that
  • (i) is labeled for such use, and
  • (ii) contains the same active ingredient in the dosage form and concentration necessary for treatment; or, in cases where there is an approved new animal drug, the approved drug is clinically ineffective (see #7) for the use for which the medicated feed is intended;
Extralabel Use
CPG 615.115

• Considerations
  – Veterinarian
    • General
    • OTC Medicated Feed
    • VFD Medicated Feed
Extralabel Use
CPG 615.115

• Considerations
  – Veterinarian
  • OTC Medicated Feed
    – All conditions in General Considerations and in Veterinarian Considerations/General, and
    – Written recommendation including the medical rationale dated within the 6 months prior to use.
    – Provide a copy of recommendation to the client
    – DVM keep a copy of the recommendation to show to FDA on request.
Extralabel Use
CPG 615.115

• **Considerations**
  – Veterinarian
  
  • **VFD Medicated Feed**
    – All conditions in General Considerations and in Veterinarian Considerations/General, and
    – Written recommendation including medical rationale dated within the 6 months prior to use.
    – Provide a copy of recommendation to the client
    – Keep a copy of recommendation for at least 2 years to show to FDA on request.
Extralabel Use
CPG 615.115

• C. Veterinary Considerations
  • Veterinary Feed Directive (VFD) Medicated Feed

• Completed the VFD consistent with the approved labeling for the approved species, indication etc. Then in the "Special Instructions" the veterinarian should note:
  – a. "This VFD is being issued in accordance with CPG 615.115";
  – b. The actual species for which the medicated feed is intended (unless that species is already reflected on the VFD because the VFD drug is approved for use in that minor species, but is being used for a different indication); and
  – c. The withdrawal time associated with the extralabel use if different than the labeled withdrawal time as already reflected on the VFD (see section C. Veterinarian Considerations/General).
Extralabel Use
CPG 615.115

• Policy Statement

• Considerations
  – General
  – Veterinarian
  – Producer
  – Distributor/Manufacturer
Extralabel Use
CPG 615.115

• In general, the Agency will not recommend or initiate enforcement action against
  • the veterinarian,
  • animal producer,
  • feed mill, or other distributor
• when extralabel use is consistent with this document.
Extralabel Use
CPG 615.115

• E. Regulatory Action Guidance

• Warning Letter(s)

• Domestic Seizure
Outline

• Take Home

• Changes to Affected Products
  Changes to Oral Dosage Form Products
  Changes to Medicated Feed Products
  • Major & Minor Species

• Sources of Information

• Take Home
Sources of Information

Approved Applications: AnimalDrugs@FDA:
https://animaldrugsatfda.fda.gov/adafda/views/#/search

BlueBird labels:
http://www.fda.gov/AnimalVeterinary/Products/AnimalFoodFeeds/MedicatedFeed/BlueBirdLabels/ucm081795.htm

eCFR: http://162.140.57.127/cgi-bin/ECFR?page=browse

VFD Distributors & Licensed Feed Mills:
http://www.fda.gov/downloads/AnimalVeterinary/Products/AnimalFoodFeeds/MedicatedFeed/UCM096059.pdf
http://www.fda.gov/downloads/AnimalVeterinary/Products/AnimalFoodFeeds/MedicatedFeed/UCM089534.pdf
Sources of Information

CPG 615.115:

OMUMS:
http://www.fda.gov/animalveterinary/resourcesforyou/animalhealthliteracy/ucm189540.htm

GFI # 191:

Questions:
AskCVM@FDA.HHS.GOV
Outline

• Take Home
• Voluntary changes of Affected Products
  Changes to Oral Dosage Form Products
  Changes to Medicated Feed Products
    • Major & Minor Species
• Sources of Information
• Take Home
Take Home
All drug sponsors have aligned all affected applications with the GFI # 213 recommendations by the January 2017 target date.
Take Home

The applications impacted by these voluntary changes represent about 95% of the sales of medically important antimicrobials for reporting year 2015.
Take Home
CVM encourages veterinarians treating sheep and goats to read and follow

1. 21 CFR Part 530 regarding ELU of Rx drugs,

and

2. the considerations in CPG 615.115 regarding ELU of Medicated Feed.