

Medically Important Antimicrobials in Animal Agriculture

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Sheep

Mike Murphy DVM, JD, Ph.D., DABVT, DABT

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84 were completely withdrawn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Production (e.g., growth promotion) indications associated with medically important antimicrobials were withdrawn from all applications that included such indications for use.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

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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 *E. coli* and bacterial pneumonia (shipping fever complex) caused by *P. multocida* susceptible to oxytetracycline.

Changes to Affected Products

- Rx – Examples
 - 21 CFR Part 520.1484

- Neomycin – (Sheep & Goats)
 - A 200-113 A 200-289
 - A 200-130 A 200-378
 - A 200-235 A 200-379
 - 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

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

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>

Outline

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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

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

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
 - <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-afda-ice/documents/webcontent/ucm074659.pdf>



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

Active Ingredient	Proprietary Name	NADA/ANADA	Label Type	Indications	Marketing Status
Decoquate (liquid)	DECCOX	N039-417	Type B	For the prevention of coccidiosis in young goats caused by <i>Eimeria christenseni</i> and <i>E. ninakohlyakimovae</i> .	OTC
Decoquate	DECCOX	N039-417	Type C	For the prevention of coccidiosis in young goats caused by <i>Eimeria christenseni</i> and <i>E. ninakohlyakimovae</i> .	OTC
Decoquate	DECCOX	N039-417	Type C	For the prevention of coccidiosis in young goats caused by <i>Eimeria christenseni</i> and <i>E. ninakohlyakimovae</i> .	OTC

Goats

OTC - examples

Active Ingredient	Proprietary Name	NADA/ANADA	Label Type	Indications	Marketing Status
Monensin	RUMENSIN	N095-735	Type C	For the prevention of coccidiosis caused by <i>Eimeria crandallis</i> , <i>E. christenseni</i> , and <i>E. ninakohlyakimovae</i> in goats maintained in confinement.	OTC
Morantel tartrate	RUMATEL	N092-444	Type C	For the removal and control of mature gastrointestinal nematode infections of goats including <i>Haemonchus contortus</i> , <i>Ostertagia (Teladorsagia) circumcincta</i> , and <i>Trichostrongylus axei</i> .	OTC



Goats/kids – excluding lactating goats/dairy females 12 months of age or older

VFD - examples

Active Ingredient	Proprietary Name	NADA/ANADA	Label Type	Indications	Marketing Status
<u>Neomycin Sulfate</u>	NEOMIX	N140-976	Type C	For the treatment and control of colibacillosis (bacterial enteritis) caused by <i>Escherichia coli</i> susceptible to neomycin.	

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



Active Ingredient	Proprietary Name	NADA/ANADA	Label Type	Indications	Marketing Status
Chlortetracycline	CHLORMAX	N046-699	Type C	For reducing the incidence of (vibrionic) abortion caused by <i>Campylobacter fetus</i> infection susceptible to chlortetracycline.	VFD (Effective 1/1/17)
Chlortetracycline	AUREOMYCIN	N048-761	Type C	For reducing the incidence of (vibrionic) abortions caused by <i>Campylobacter fetus</i> infection susceptible to chlortetracycline in breeding sheep.	VFD (Effective 1/1/17)
Chlortetracycline	CLTC	N092-286	Type C	For reducing the incidence of (vibrionic) abortions caused by <i>Campylobacter fetus</i> infection susceptible to chlortetracycline in breeding sheep.	VFD (Effective 1/1/17)
Chlortetracycline	PENNCHLOR	N138-935	Type C	For reducing the incidence of (vibrionic) abortions caused by <i>Campylobacter fetus</i> infection susceptible to chlortetracycline in breeding sheep.	VFD (Effective 1/1/17)
Chlortetracycline	DERACIN	A200-510	Type C	For reduction in the incidence of (vibrionic) abortions caused by <i>Campylobacter fetus</i> infection susceptible to chlortetracycline in breeding sheep.	VFD (Effective 1/1/17)

Sheep (Multiple Classes)

OTC - examples



Active Ingredient	Proprietary Name	NADA/ANADA	Label Type	Indications	Marketing Status
Decoquate	DECCOX	N039-417	Type C	For the prevention of coccidiosis in young sheep caused by <i>Eimeria ovinoidalis</i> , <i>E. parva</i> , <i>E. bakuensis</i> , and <i>E. crandallis</i> .	OTC
Decoquate	DECCOX	N039-417	Type C	For the prevention of coccidiosis in young sheep caused by <i>Eimeria ovinoidalis</i> , <i>E. parva</i> , <i>E. bakuensis</i> , and <i>E. crandallis</i> .	OTC
Decoquate	DECCOX	N039-417	Type C	For the prevention of coccidiosis in young sheep caused by <i>Eimeria ovinoidalis</i> , <i>E. parva</i> , <i>E. bakuensis</i> , and <i>E. crandallis</i> .	OTC
Decoquate (liquid)	DECCOX	N039-417	Type B	For the prevention of coccidiosis in young sheep caused by <i>Eimeria ovinoidalis</i> , <i>E. parva</i> , <i>E. bakuensis</i> , and <i>E. crandallis</i> .	OTC

Sheep (Multiple Classes)

VFD - examples

Active Ingredient	Proprietary Name	NADA/ANADA	Label Type	Indications	Marketing Status
<u>Neomycin Sulfate</u>	NEOMIX	N140-976	Type C	For the treatment and control of colibacillosis (bacterial enteritis) caused by <i>Escherichia coli</i> susceptible to neomycin.	

Sheep (Multiple Classes)

VFD - examples



Active Ingredient	Proprietary Name	NADA/ANADA	Label Type	Indications	Marketing Status
<u>Neomycin Sulfate and Oxytetracycline</u>	NEO-TERRAMYCIN	N094-975	Type C	Treatment of bacterial enteritis caused by <i>Escherichia coli</i> and bacterial pneumonia caused by <i>Pasteurella multocida</i> susceptible to oxytetracycline; treatment and control of colibacillosis (bacterial enteritis) caused by <i>E. coli</i> susceptible to neomycin	VFD (Effective 1/1/17)
<u>Neomycin Sulfate and Oxytetracycline</u>	NEO-OXTC	N138-939	Type C	Treatment of bacterial enteritis caused by <i>Escherichia coli</i> and bacterial pneumonia caused by <i>Pasteurella multocida</i> susceptible to oxytetracycline; treatment and control of colibacillosis (bacterial enteritis) caused by <i>E. coli</i> susceptible to neomycin	VFD (Effective 1/1/17)

Sheep (Multiple Classes)

VFD - examples



Active Ingredient	Proprietary Name	NADA/ANADA	Label Type	Indications	Marketing Status
Oxytetracycline	TERRAMYCIN	N008-804	Type C	For treatment of bacterial enteritis caused by Escherichia coli and bacterial pneumonia caused by Pasteurella multocida susceptible to oxytetracycline.	VFD (Effective 1/1/17)
Oxytetracycline	OXTC	N095-143	Type C	For sheep for treatment of bacterial enteritis caused by Escherichia coli and bacterial pneumonia caused by Pasteurella multocida susceptible to oxytetracycline.	VFD (Effective 1/1/17)
Oxytetracycline	OTC	N138-938	Type C	For treatment of bacterial enteritis caused by Escherichia coli and bacterial pneumonia caused by Pasteurella multocida susceptible to oxytetracycline.	VFD (Effective 1/1/17)

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

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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

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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:

<http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-afda-ice/documents/webcontent/ucm074659.pdf>

OMUMS:

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

GFI # 191:

<http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052460.pdf>

Questions:

AskCVM@FDA.HHS.GOV

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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.

