Navigating Drug Therapy for Dairy Goats

2021 Dairy Goat Webinar Series
September 22, 2021

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Definitions
Medically Important Antimicrobial Drugs
Source: US FDA – Guidance for Industry (GFI) 152

- Critically Important
  - 3rd Generation Cephalosporins (Ceftiofur - in FA’s)
  - Fluoroquinolones
  - Macrolides
  - Trimethoprim/Sulfa

- Important
  - Everything else

- Highly Important
  - Penicillins
  - Tetracyclines
  - Phenicols

- Not Important
  - Ionophores
  - Bambermycins
  - Bacitracin

Currently considering amending this group of drugs – current suggested reclassification increases importance of many drugs – i.e. penicillins, tetracyclines (grouped)
Major vs Minor FA Species

• **Major**: Cattle, pigs, chickens, and turkeys

• **Minor Use Species**: All other animal species food animal species

• Regardless of use – pet’s are food animals if traditionally considered a food or fiber species
# Production Classes - FDA

**FDA Link to Production Classes for Major Food Producing Species**

<table>
<thead>
<tr>
<th>Major Subclass</th>
<th>Subclass</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veal Calves</td>
<td>none</td>
<td>Immature male or female cattle intended for slaughter for veal production. Most are pre-ruminating; but depending on management, age and diet, may be ruminating.</td>
</tr>
<tr>
<td>Veal Calves</td>
<td>Bob Veal</td>
<td>Veal calves less than 2 weeks of age and pre-ruminating.</td>
</tr>
<tr>
<td>Beef Calves</td>
<td>none</td>
<td>Beef cattle (beef breeds only) nursing their dams from birth until weaning. May be pre-ruminating or ruminating. Formerly referred to as “suckling beef calves”. Excludes veal calves.</td>
</tr>
<tr>
<td>Beef Calves</td>
<td>Beef Calves less than 2 months of age</td>
<td>Beef calves considered pre-ruminating and nursing their dams from birth until 2 months of age.</td>
</tr>
<tr>
<td>Beef Calves</td>
<td>Beef Calves 2 months of age and older</td>
<td>Beef calves considered ruminating and nursing their dams from 2 months of age to weaning.</td>
</tr>
<tr>
<td>Dairy Calves</td>
<td>none</td>
<td>Pre-ruminating dairy cattle from birth until weaning being fed a ration that includes milk or liquid milk replacer. Excludes veal calves.</td>
</tr>
</tbody>
</table>
Lactating Dairy Cow

- **Dairy industry definition**: A dairy breed cow that is producing milk

- **FDA definition**: A dairy breed animal that is 20 months of age and older.
  - Lactating or dry

***No similar FDA definition for lactating doe or ewe.***
Residue – Violative vs Non-Violative

• Residue:

• Violative residue:
CONTAINS NON-BINDING RECOMMENDATIONS

Guidance for Industry

GENERAL PRINCIPLES FOR EVALUATING THE SAFETY OF COMPOUNDS USED IN FOOD-PRODUCING ANIMALS

(This version of the guidance replaces the version that was made available in June 21, 2005. This guidance document has been revised to correct the contact information in regard to this document.)

Comments and suggestions may be submitted anytime to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. Comments may also be submitted electronically on the Internet at http://www.regulations.gov All written comments should be identified with Docket No. 2005D-0219.

For questions regarding this document, contact the Division of Human Food Safety, Center for Veterinary Medicine, (HFV-150), Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, 240-276-8211.

Additional copies of this guidance document may be requested from the Communications Staff (HFV-12), Center for Veterinary Medicine, Food and Drug Administration, 7519 Standish Place, Rockville, MD 20855 and may be viewed on the Internet at http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine
July 25, 2006
**Regulatory Residue Limits**

**“Tolerance” & “Target Test Level”**

- **Tolerance** = Maximum *legally allowable* level or concentration of a drug or chemical in a food product at the time milk or eggs are marketed, or the animal is slaughtered.

- **Target Test Level (For Milk Only)** = Guide for deciding whether or not to prosecute. They are not and cannot be transformed into tolerances. They are not binding, do not dictate any result, do not limit the FDA’s discretion in any way, and do not protect milk producers from court enforcement action.

  \[ \text{EX} \] – Procaine Penicillin G – 5 ppb (ng/mL)
• Residue: Any substance that is foreign to the body. In our case, we are interested in residues that are left after drug administration.

• Violative residue:
Residue – Violative vs Non-Violative

- **Residue**: A substance that is foreign to the body (and products such as milk or eggs). In our case, we are interested in residues that are left after drug administration.

- **Violative residue**: A drug residue found to be at or above the regulatory limit (tolerance or target test level) in a tissue, milk (lactating animal), or eggs.

  - Residues can be violative or non-violative
Slaughter & Milk Withdrawal Times (And Eggs)

- A residue elimination study is done in the target animal species

- Statistical analysis is applied to the study data so that when the withdrawal time is reached, less than 1 in 1000 animals is likely to still have residues above the regulatory limit (tolerance) in the target tissue.
  - Target tissue – Meat – last tissue from which drug residue disappears – usually kidney or liver
    - Also in milk and eggs, if labeled for these species
Take Home Points When Using Extra-Label Use

• There can be legally acceptable residues of drugs in edible tissues, eggs, or milk at slaughter (or milk harvest) IF there is an established tolerance in tissues/milk for that animal species.
  – Non-violative residues

• For drugs without a label and corresponding tolerance in a species (including use class and edible tissue), then **ANY residue detected** is violative.

• Consult with FARAD for guidance.
**Draxxin®**
*(tulathromycin)*
Injectable Solution

**Antibiotic**

100 mg of tulathromycin/mL

For use in beef cattle (including suckling calves), non-lactating dairy cattle (including dairy calves), veal calves, and swine. Not for use in female dairy cattle 20 months of age or older.

<table>
<thead>
<tr>
<th>DRAXXIN® IS APPROVED FOR</th>
<th>PATHOGENS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRD Control and Treatment</td>
<td><em>Mannheimia haemolytica</em></td>
</tr>
<tr>
<td></td>
<td><em>Pasteurella multocida</em></td>
</tr>
<tr>
<td></td>
<td><em>Histophilus somni</em></td>
</tr>
<tr>
<td></td>
<td><em>Mycoplasma bovis</em></td>
</tr>
<tr>
<td>Treatment of Bovine Foot Rot</td>
<td><em>Fusobacterium necrophorum</em></td>
</tr>
<tr>
<td></td>
<td><em>Porphyromonas levii</em></td>
</tr>
<tr>
<td>Treatment of Pinkeye</td>
<td><em>Moraxella bovis</em></td>
</tr>
</tbody>
</table>

Food Supply Veterinary Medicine
Veterinary Diagnostic and Production Animal Medicine
Iowa State University
Detecting Drug Residues in Milk from Small Ruminants

• In dairy cattle, milk drug residues monitored on each load of milk delivered to a processing plant.

• SR milk would be monitored with the same technology.
Extra-Label Drug Use

• AMDUCA = Animal Medicinal Drug Use Clarification Act.
• Legalized extra-label use of approved drugs by licensed veterinarians.
• 1996
AMDUCA Requirements

• Permitted only by or under the supervision of a licensed veterinarian.
• Only FDA approved animal and human drugs.
• Therapeutic purposes only – animal’s health is suffering or threatened.
  – Cannot enhance production
• Valid veterinarian/client/patient relationship must be in place.
• Specific Record Requirements.
Specific Label & Record Requirements

Label Requirements:

- Name and address of the prescribing veterinarians;
- Established name of the drug;
- Any specified directions for use including the class/species or identification of the animal or herd, flock, pen, lot, or other group; the dosage frequency, and route of administration; and the duration of therapy;
- Any cautionary statements restricting use to a licensed veterinarian (Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.);
- For food-producing species: Your specified withdrawal, withholding, or discard time for meat, milk, eggs, or any other food product originating from the treated animal(s).

Record Requirements:

- Identify the animals, either as individuals or a group;
- Species of animal(s) treated;
- Number of animals treated;
- Medical conditions being treated;
- The established name of the drug and active ingredient;
- Dosage prescribed or used;
- Route of administration;
- Duration of treatment;
- Specified withdrawal, withholding or discard time(s), if applicable for meat, milk, eggs, or animal derived food products;
- Records must be kept for a minimum of 2 years after treatment (Check your state requirements regarding record retention rules.);
- The FDA must be allowed access to these records to estimate risk to public health.

Source: AVMA ELDU Algorithm
AMDUCA Requirements

• Only in drugs administered parentally, intramammary, topically, or in water. Extra-label use in feeds is prohibited.

• Cannot result in a violative food residue or a residue that may affect public health.
  – Extended withdrawal period required

• AVMA Algorithm

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WELCOME TO FARAD

FARAD is a congressionally-mandated risk-management program that is supported by the United States Department of Agriculture (USDA). In view of limited resources, FARAD's focus is limited to food animal species exclusively. The program is maintained by a consortium of universities, including University of California-Davis (UCD), University of Florida (UF), Kansas State University (KSU) and North Carolina State University (NCSU). FARAD's primary mission is to prevent or mitigate illegal or harmful residues of drugs, pesticides, biotoxins and other chemical agents that may contaminate foods of animal origin.

CLICK HERE to view details and download instructions with regard to our new Android App, available now, in the Google play store.

CLICK HERE to submit a question or receive advice regarding residue avoidance or mitigation.

CLICK HERE to search VetGRAM for FDA approved food animal drugs or to access our mobile-friendly VetGRAM, optimized for the iPad and other handheld devices.

CLICK HERE to search FARAD-recommended withdrawal intervals (WDI) for extra-label use of approved food animal drugs.

www.farad.org
US Prohibited Drug Use-Food Animals

Drugs PROHIBITED from ANY use:

- Chloramphenicol
- Clenbuterol
- Diethylstilbesterol
- Dimetridazole
- Ipronidazole
- Other Nitroimidazoles
- Furazolidone, nitrofurazone, other nitrofurans.
Prohibited for Extra-Label Use

- **Sulfonamide** drugs in lactating dairy cows (except approved use of sulfadimethoxine, sulfabromomethazine, & sulfaethoxypyridazine.)
  - Pneumonia
  - Foot rot

- Phenylbutazone in female dairy cattle 20 months of age or older.

- Glycopeptides (vancomycin)
Prohibited for Extra-Label Use

Fluoroquinolones

• Enrofloxacin – Baytril 100, Enroflox 100
  – Respiratory diseases only – cattle
  – Respiratory disease and colibacillosis in weaned swine
  – may NOT be used in female dairy cattle - >20 m

• Danofloxacin – beef cattle respiratory disease only – not dairy

![Advocin](image)
Prohibited for Extra-Label Use

• **Cephalosporins**-NO extra-label use in major food producing species (cattle, swine, chickens, or turkeys):
  – Cannot be used for disease prevention purposes;
    • *(See AVMA Definitions of Prevention, Control, and Treatment)*
  – Cannot be used at unapproved doses, frequencies, durations, or routes of administration; or
  – Cannot be used if the drug is **not approved** for that species and production class (major classes only)
Cephalosporin Prohibition

The following *exceptions to the prohibition* apply:

- Extra label use of approved cephalapirin products in food-producing animals (IMM only in US);
- Use to treat or control an extra-label *disease indication*, as long as this use adheres to a labeled dosage regimen (i.e., dose, route of administration, frequency, and duration of use).
- Extra label use in food-producing *minor species*, such as ducks or rabbits.
US Grade “A” Dairy Farms

• No allowed use or storage of the following drugs on dairy farms:
  – Non-medical grade DMSO (dimethylsulfoxide)
  – Dipyrone
  – Colloidal Silver
Veterinary Feed Directive (VFD)

• An order for utilizing “medically important” antibiotics in animal feed.
  – Technically not a script, but functionally works the same

• It requires a VFD from a veterinarian who the producer has a valid VCPR with for their operation.
  – Veterinarian is responsible for filling it our correctly, based on the correct information the producer gets to them.

• Producer (or the veterinarian) will deliver the VFD to the feed mill to manufacture the feed.
VFD Scope

• No extra-label usage!

• What about minor use species?
Sec. 615.115 Extralabel Use of Medicated Feeds for Minor Species

Compliance Policy Guide

Guidance for FDA Staff

Contains Nonbinding Recommendations
Minor-Use Species - CPG 615.115

• “.... the FD&C Act does not permit extralabel use of drugs in animal feed...

• However, when there are no approved treatment options available and the health of animals is threatened, and suffering or death would result from failure to treat the affected animals, extralabel use of medicated feed may be considered for treatment of minor species. Because of the need to have therapeutic options available for treatment of minor species, and to help ensure animal safety and human food safety, FDA is issuing this revised CPG to provide guidance to FDA staff with respect to factors to consider when determining whether to take enforcement action against a veterinarian, animal producer, feed manufacturer, and/or feed distributor for the extralabel use of OTC and VFD medicated feeds in minor species.”
“Extra-label use of medicated feeds is illegal. This guide does not make extra-label use legal or allow unapproved medicated feeds to be promoted or marketed for these uses. It simply makes it less likely that action will be taken against veterinarians and producers who use medicated feeds approved for use in other species for therapeutic purposes in minor species under the conditions stated in the CPG.”
Requirements

1. Must have a valid Veterinary-Client-Patient-Relationship
   – CPG references FDA definition of VCPR

2. Ascertained that there is no therapeutic dosage form that can be practically used under legal extralabel use
   – Use of CTC for Vibrio abortion in sheep – 80 mg/hd/day

3. Provide express written recommendations prior to use
Requirements

4. The feed antimicrobial must be approved in a species similar to desired species
   - Mammalian species for SR’s
   - Cannot be a prohibited drug per FDA
5. Limited to farmed or confined species
6. Not for improved rate of gain or feed efficiency
7. Cannot promote use
8. Extend withdrawal time to prevent residue
What about milk and milk replacer?

- Milk / milk replacer is a feed
- Any use of a medically important antibiotic in milk replacer must be authorized through a VFD
- Only feeding according to the label is allowed.
  - Neomycin and/or oxytetracycline
  - Limit of 7-14 days per label.
Water-soluble medications

• Not regulated as VFD medications
• Water-soluble medications have moved from OTC to prescription classifications.
  – Veterinary prescription needed or buy directly from veterinarian.
• Extra-label use permissible.
Commonly Used Pharmaceuticals in Dairy Goats
Intramammary Antibiotics – Cephapirin (Today)

- Geometric mean maximum CEPH concentration in milk was 22.8 µg/mL (range = 2.7 - 77.7 µg/mL) occurring at a $T_{\text{max}}$ of $30 \pm 10.6$ h (mean ± SD).
- The mean CEPH concentration dropped below the US tolerance for cattle of 0.02 µg/mL between 72-120 h after the final IMM administration.

Our Current Research

- IMM antibiotics can be useful for improving milk quality
- Based on data from Hayman et. al, USDA funded a project to evaluate dry cow products in dairy goats:
  - Establish withdrawal times for 2 common IMM antibiotics.
  - Evaluate potential for antimicrobial resistance.
  - Develop outreach opportunities to facilitate safe, effective use on-farms.

If you are interested in learning more about this project or getting involved let us know.
USDA Goat Study Info

Cephapirin Benzathine (Tomorrow) vs Cloxacillin (Orbenin DC)

– Meat withdrawal data – in progress
– Milk withdrawal data – coming Spring 2022

Currently both extra-label use – any detectable residue is violative.

– Test milk from fresh does before processing

Stay tuned for data!
Selecting the Right Drug
“SPACED”

- **S**pectrum – Is the drug effective against the pathogen
- **P**K/PD – Can I get the drug to the location >MIC
- **A**dverse reactions – Is the drug safe?
- **C**ompliance – Is it legal, can I use in extra-label manner
- **E**nvironment – aerobe/anaerobe/ pus / acidic / basic
- **D**iagnostics / Break points - AST
Drugs Approved for Dairy Goats

• 28 FDA approved drugs for goats
  – 4 approved for lactating goats
  – 4 additional approved for non-lactating

http://www.farad.org/vetgram/goats.asp
# Drugs Approved for Lactating Dairy Goats

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Approved Use(s)</th>
<th>Route of Administration</th>
<th>Meat Withhold</th>
<th>Milk Withhold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftiofur Sodium (Naxcel, Ceftiflex)</td>
<td>Respiratory disease</td>
<td>IM</td>
<td>0 days*</td>
<td>0 hours*</td>
</tr>
<tr>
<td>Thiabendazole (Equizole, EZ-EX pellets, Omnizole)</td>
<td>Intestinal parasites</td>
<td>Oral</td>
<td>30 days</td>
<td>96 hours (4 days)</td>
</tr>
<tr>
<td>Neomycin Sulfate</td>
<td>Bacterial enteritis</td>
<td>Oral</td>
<td>3 days</td>
<td>0 hours</td>
</tr>
<tr>
<td>Moranetl (Rumantel 88)</td>
<td>Intestinal parasites</td>
<td>Oral</td>
<td>30 days</td>
<td>0 hours</td>
</tr>
</tbody>
</table>

*Note: The tolerance of Ceftiofur decreased since its original approval. Goat-side testing is recommended before processing.
# Drugs Approved for Non-Lactating Goats

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Approved Use</th>
<th>Route of Administration</th>
<th>Meat Withhold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albendazole (Valbazen)</td>
<td>Removal &amp; control of liver flukes</td>
<td>Oral</td>
<td>7 days</td>
</tr>
<tr>
<td>Fenbendazole (Panacur)</td>
<td>Control of stomach worms</td>
<td>Oral</td>
<td>6 days</td>
</tr>
<tr>
<td>Monensin Sodium (Rumensin)*</td>
<td>Prevention of coccidiosis</td>
<td>Oral</td>
<td>0 days</td>
</tr>
<tr>
<td>Decoquinate (Deccox)*</td>
<td>Prevention of coccidiosis</td>
<td>Oral</td>
<td>0 days</td>
</tr>
</tbody>
</table>

*Feed only to goats maintained in confinement*

All drugs approved for lactating goats are also acceptable in non-lactating goats.
Flunixin Meglumine (Banamine, Prevail)

- Meat withhold: 10 days
- Milk withhold: 72 hours (3 days)
- Route: IV or IM
- Uses: Pain & inflammation, fever reducer
- Pour-on not recommended – low bioavailability.
- Oral paste is available but less effective than injectable.


Meloxicam

- Meat withhold: 15 days
- Milk withhold: FARAD request
- Route: Oral
- Uses: Pain & inflammation, fever reducer

More data needed to establish accurate milk withdrawal times.

Other pain medications

Phenylbutazone (Bute)
- Prohibited in dairy cattle.
- Not recommended in dairy goats

Ketoprofen
- Used on dairy cattle and goats in other countries.
- May be cost-prohibitive in US
- Need more data to establish appropriate withdrawal times, current recommendations based on cattle.

Aspirin
- Meat withhold: 1 day
- Milk withhold: 24 hours
- Route: Oral
- Poor absorption, relatively high doses required.

Oxytetracycline (LA 200)

Long-acting

- Meat withhold: 35 days
- Milk withhold: 144 hours
- Route: SC
  - Painful on injection SC
  - For short acting formulations, FARAD request recommended.
  - IV administration has been associated with anaphylaxis
- Uses: Pinkeye, respiratory disease

Procaine Penicillin G

- Meat withdrawal: 9 days
- Milk withdrawal: 96h – Test before processing
- Route: IM
- Most veterinarians recommend higher than label dosing.

- Withdrawal data is inconsistent
  – FARAD does not offer recommendations for this product in small ruminants.

Caution: Penicillin residues can cause anaphylactic reactions in humans that consume them.

Ceftiofur

Naxcel & Excenel (short acting)
- Meat withhold: 0 days
- Milk withhold: 0 days
- Route: IM
- Approved Uses: Respiratory disease

Excede (long acting)
- Withdrawal times: FARAD request
- Route: SQ at base of ear

Date of approval - March 7, 2001.
Dewormers

• Regulated by EPA, not USDA
• Any extra-label use is forbidden in food animals
• Due to growing resistance to dewormers, routine fecal evaluations should be used to determine appropriate medications for each herd.
“Yes ... I believe there's a question in the back.”

Questions: pgorden@iastate.edu
Questions?

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