The FDA specifies all animal drug label contents

- **Drugs**: Antibiotics, hormones, antihelmentics
- **7 Items**:  
  - Animal Species  
  - Disease Condition  
  - Route of Administration  
  - Dosage Amount  
  - Administration Frequency  
  - Duration of Administration  
  - Withdrawal Period (food animals)

Understanding the FDA’s approach to drug regulation

The FDA has the legal authority to regulate:  
- All animal drugs  
- All medical devices

This is a “medical device” under the law

The FDA classifies drugs two ways

**OTC** - (Over-the-Counter)  
- purchase anywhere (feed store, ...)  
- *used by producer only according to label instructions*

**Prescription** (Rx, Legend)  
- purchase only from pharmacies by prescription or from veterinarians  
- *used only under a veterinarian’s instructions with valid VCPR*

The FDA is required to classify a drug OTC if two conditions can be met

- if “adequate directions for use” can be prepared for a layperson to use the drugs  
  - safely  
  - effectively  
- Prevented by toxicity, harmful effects, method of use

For FDA approval, a manufacture must show that the drug is **safe**

- for the treated animal  
- for persons administering the drug  
- for the environment  
- in food products derived from the animal
FDA defines effectiveness three ways

- Accurate diagnosis can be made with reasonable certainty
- Drug can be properly administered
- Disease course can be followed to assess treatment success

If any of these cannot be done by the average lay person, the drug cannot be OTC

Federal Law forbids any off-label use by non-veterinarians

*Any* extra-label (non-label dosage, condition, species, ...) use by a non-veterinarian is illegal, OTC or Legend!

Penalties on the involved parties are up to a $500,000 fine and 1 year imprisonment
Extra-Label (Off-Label) Use (ELU)

- “The use of any drug (OTC or Rx) in any manner that is not in accordance with the FDA approved label directions”

- 7 Label Items:
  - *species, condition, dosage*, route, frequency, duration, withdrawal
  - Dogs, cats, horses, sheep, goats, camelids, fish, . . .

Rx (Legend) drugs have a specific legend

- Official FDA Rx Legend:
  - *Caution*: Federal law restricts this drug to use by or on the order of a licensed veterinarian

- Any other wording is an “ethical” drug for marketing purposes
  - “For Veterinary Use Only”, “Sold to Veterinarians only”

Legend is at the top of the package insert

FDA law specifies 6 specific extra-label use conditions

*Only by veterinarians only when:*

- Diagnosis is made within a valid VCPR
- No FDA-approved drug for the condition or the approved dose is ineffective
- Animal ID is recorded for 2 years
- *The animal’s health* is in immediate danger
- Drug is properly labeled
- Withdrawal time is increased to prevent residues

The FDA specifies 3 parts of valid VCPR

*A valid VCPR exists when the veterinarian:*

- agrees to be responsible for making clinical judgments and the client agrees to follow the instructions
- is knowledgeable of the animals, their care, and keeping and has made medically appropriate and timely premise visits
- is readily available for follow-up evaluation
The FDA specifies 5 parts of proper ELU labeling

- Veterinarian’s name, address, phone number
- Active drug ingredients
- Directions for use (condition, species, dose, route, frequency, duration, withdrawal)
- Cautionary statements
- Veterinarian’s specified withdrawal/discard times for meat and milk

The FDA retains regulatory discretion to prosecute violations

- Veterinarians (and clients) may be subject to regulatory action for any violative residues in human food resulting from their prescriptions, recommendations or treatments contrary to approved label instructions in violation of AMDUCA
- They will be subject to regulatory action for any detected use of banned drugs

The FDA bans the use of some drugs in food animals

Drugs banned from use in food animals under any circumstances:
- Chloramphenicol
- Clenbuterol
- Diethylstilbestrol (DES)
- Fluoroquinolones (except as specifically approved)
- Glycopeptides
- Nitroimidazoles (Dimetridazole, Ipronidazole)
- Nitrofurazone, Furazolidone (Used to exclude topical use)

The FDA restricts the extra-label use of certain drugs in food animals

Modified Legend:

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian
Federal law prohibits the extra-label use of this drug in food-producing animals

Examples of drugs banned from extra-label use in food animals:
- Baytril
- Pfizer A180
- Pfizer Zeniquin

Why the particulars?

Complicated effects:
- Differences between species
- Differences between routes and administration frequency
- Problems with withdrawal times

The background behind why these regulations are in place

Drug serum levels differ between species
Serum drug levels differ by administration route

**Figure 3. OTC blood serum levels, 5 mg/lb. b.w.**

Antibiotic efficacy is determined by these levels

Withdrawal Period: *What is it?*

*Time required for a drug residue to reach safe concentrations in edible tissues*

Once a drug is given, it *never* reaches zero concentration

*Zero residues are a scientific impossibility after use*

*For this reason, cancer-causing drugs can never be used in food animals (Delaney Amendment to Food and Drug Act)*

Withdrawal Period: *How is it established?*

*After drug efficacy is established, the manufacture:*

1. Determines the amounts of the drug and its metabolites in edible tissues over time
   - Milk
   - Muscle
   - Kidney
   - Liver
   - Fat

**Half-life Elimination Curve**

For every “half-life”, ½ of the remaining residue is removed

One Day
Two Days
Three Days

**DAYS WITHDRAWAL**

PARTS PER MILLION

**Milk**
**Muscle**
**Kidney**
**Liver**
**Fat**
The manufacturer establishes testing methods for the FDA to use in residue testing

Sensitivity of common testing methods:
- 1 drop in 13,000 gallons of water
- 1.5 inches in the circumference of the earth (24,860 miles)

Some drugs can’t be marketed because testing methods aren’t sensitive enough

The toxic effects of the drug are determined by studies in lab animals

3. Special lab studies establish the toxicological effects of the drug and its metabolites
   - Lifetime studies in rats and mice (2 years)
   - Non-rodent mammalian study (usually dogs)
   - 3 generation reproductive study for birth defects
   - Other special studies as indicated by the type of drug

From toxic effect data, allowable human food levels are established

4. From the laboratory exposure data, acceptable daily intake (ADI) levels from edible tissue for “no effect” in humans are established with the safety margins:
   - Birth defects: 1:1,000 safety margin
   - Carcinogens: None allowed
   - Other effects: 1:100 safety margin

Drug approval testing costs $25 million or more
Adding a label claim costs $2.5 to $10 million

Why is beef quality assurance a big deal?

Subtitle: How does the FDA detect illegal drug use?

Injection lesion pictures 24 hours post-injection with the label drug amount by the label IM route
Other injection lesion examples:

Visibly affected areas are trimmed and the carcass is held pending test results.
Medicated feeds cannot be used off-label

- Extra-label use (AMDUCA) does not apply to feeds
- Drugs may be added to feeds only at FDA approved levels

The FDA PMO also regulates drug use on dairy farms

The FDA Grade “A” Pasteurized Milk Ordinance (PMO) also dictates that drugs on a dairy farm must:
- Meet the FDA labeling requirements and extra-label use conditions
- Be stored to minimize the potential for milk contamination (lactating cow drugs separated from the others)

All milk is tested for drug residues

Several forms of drug use are common but illegal

- Producer use of OTC drug "off label"
- Producer / veterinarian
  - Adding antibiotics to milk replacer
    • "Extra-label" use in feed is illegal!
  - Using special list drugs "off label" (ELU)
    • Bayer Baytril, Pfizer A180
- Industry consequence – potential removal of product from market

Web Notes - Read:

**Conditions for Producers’ Use of Livestock Drugs**
http://www.vetmed.wsu.edu/courses-jmgay/VMADProducerDrugs.htm

**Sanitation in the control of livestock infectious disease**
http://www.vetmed.wsu.edu/courses-jmgay/FDIUSanitation.htm

**Epidemiology Concepts for Disease in Animal Groups**
http://www.vetmed.wsu.edu/courses-jmgay/EpiMod2.htm

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