Food Animal Drug Use, Misuse and Residues

# Definitions

**Extra-Label Drug Use (ELDU)** Use of a drug other than exactly as described on the manufacturer’s label. This label must include indication, dose, and frequency of administration or route of administration.

**AMDUCA** The Animal Medical Drug Use Clarification Act defines the circumstances under which veterinarians may prescribe or dispense or use drugs extra-label. [www.avma.org/reference/amduca/amduca1.asp](http://www.avma.org/reference/amduca/amduca1.asp)

**Veterinary Feed Directive drugs (VFD)** A veterinarian’s order delivered to the feed mill is required for these drugs to be included in the feed delivered to the farm. There is no ELDU for VFD drugs.

**Banned Drugs** Drugs that are banned from use in any food animal or any animal who’s products may enter human food.

**FARAD** Food Animal Residue Avoidance Databank. A database which provides information on approved veterinary drugs, but also provides information on withdrawal times and residue information for drugs given extra-label. [www.farad.org](http://www.farad.org)

**Violative Residue** Drug levels in meat or milk that are above the safe or tolerant levels defined by FDA.

**Assurance Programs** Livestock industry sponsored educational and certification programs aimed at reducing violative residues and carcass quality problems such as injection site abscesses.

**Pasteurized Milk Ordinance** The set of regulations agreed at the Interstate Milk Shipper’s Conference(IMS) which define the way in which milk may be produced. Includes regulations for drug use and storage on farms. FDA, State and federal Veterinarians and industry groups are represented on the IMS.

**Labeled alternative** If a comparable approved (labeled) drug is available a non-approved similar drug may not be used extra-label.

**Over the Counter Drugs (OTC)** Some antibiotics are available for the public to buy directly (e.g. from farm supply stores). Procaine Penicillin G is an example. The public can use these drugs to treat their own animals, but only exactly as described on the manufacturer’s label. Veterinarians may use the drugs extra label.

**Prescription Drugs** Prescription Drugs are always marked with the statement:

“CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.” Prescription drugs are only available from veterinarians or by veterinary prescription. Veterinarians may use prescription drugs extra label as long as they meet the regulations for ELDU, and as long as extra-label use of the drug is not specifically prohibited.

**The Precautionary Principal** The precautionary principle states that if an action or policy has a suspected risk of causing harm to the public or to the environment, in the absence of scientific consensus that the action or policy is harmful, the burden of proof that it is *not* harmful falls on those taking the action. Under European law the application of the precautionary principle is a statutory requirement. The European Union has banned the use of hormonal growth promotants used in the US beef industry under this principle, and prevented the export of US beef to Europe.

# Requirements for Extra-Label Drug Use

* 1. Valid veterinarian/client/patient relationship (VCPR)
	2. No labeled drug alternative available
	3. Adequate records are kept by veterinarian and client
	4. Significantly prolonged withdrawal times
	5. Properly labeled by veterinarian

\*There is no extra label privilege for drugs added to feed. Drugs added to feed can only be used exactly as described on the manufacturer’s label

AVMA has an on-line [decision making algorithm](http://www.avma.org/reference/amduca/amduca2.asp) for extra- label drug use

## Extra-Label Drug Use Label

What must be on the label:

1. Name and address of the veterinarian
2. Established name of the drug
3. Any specified directions for use including the class/species animal or herd ID, flock, pen, lot, or other group; the dosage frequency, and route of administration; and the duration of therapy
4. Any cautionary statements
5. Your **specified withdrawal**, withholding, or discard time for meat, milk, eggs, or any other food. You must specify a withdrawal time.



# Potential Risks to Humans from Drug Residues in Meat or Milk

**Potential Risks to Humans**

Direct poisoning by Drug Residues

Cancer

Mutations

Allergic Reactions

Bacterial Drug Resistance

Effects on Food Processing

### Direct Poisoning by Drug Residue

This may be as a result of:

1. toxicity or
2. the drug exercising its pharmacologic effect

**Toxicity examples:**

1. Chloramphenicol. Chloramphenicol triggers the development of aplastic anemia in humans. This is a non-dose dependent toxicity – the chloramphenicol acts as a trigger.
2. Dihydrostreptomycin causes optic neuritis and other neuropathies.
3. Furazolidone can cause cardiomyopathies – although blood levels fall rapidly some metabolites seem to be more or less permanently tissue bound.

**Pharmacologic effect examples:**

1. Perturbation of gut flora by tetracycline or erythromycin. Oral antibiotics can inhibit gut bacteria which metabolize some of the digoxin given orally to heart patients. In patients treated with oral doses of erythromycin or tetracycline digoxin blood levels may rise by up to 100% leading to digtalis toxicity. However, it is not proven that this occurs at sub-therapeutic antibiotic levels
2. Consumption of tissues, particularly liver, from animals treated with the B agonist clenbuterol can lead the drug exercising its pharmacological effects in consumers. It has been illegally administered to cattle as a growth promotant. Clenbuterol (Ventipulmin) is available for veterinary use and is labeled for use as a broncho-dilator in horses.

### Cancer

1. Between 1940 and 1970 women with histories of miscarriages were treated with DES (diethyl stilbestrol) during subsequent pregnancies, in the belief that it would help to maintain the pregnancy. Daughters of these women developed vaginal adenocarcinomas as a result of exposure to the drug in utero.
2. Nitrofurans (such as furazolidone and nitrofurazone) have been shown to cause ovarian cancer in rats.

### Mutations

1. Nitroimidazoles (Dimetridazole, Metronidazole *[Flagyl]*, Ipronidazole) are potent mutagens and potential carcinogens

### Allergic Reactions

It has been difficult to document allergic sensitivity developing *de novo* in humans as a result of antibiotic use in animals although there is evidence of allergic responses in individuals who are already sensitive.

1. 58% of patients with hives as a result of penicillin allergy had remission of symptoms when taken off milk.
2. There is a report of a 14 year old girl who was sensitive to streptomycin having anaphylactic reactions on four occasions after eating beef.

### Bacterial Drug Resistance

This is a highly controversial area with many competing claims over the development of drug resistance as the result of antibiotic use in animals. Sub-therapeutic use of antibiotics as growth promotants or to control endemic infections has come under particular scrutiny.

Much of the focus has been on the use of fluoroquinolones and macrolides such as virginiamycin in swine and poultry production. The issues are complex.[[1]](#footnote-1)

### Effects on Food Processing

Early antibiotic residue control programs had nothing to do with the protection of human health. They were aimed at reducing the effect of antibiotic residues in milk on the bacterial starter used in cheese production.

# FDA's Prohibited Drug List

**Banned in all food animals**

DES

Chloramphenicol

Nitroimidazoles

Nitrofurans

Clenbuterol

Dipyrone

Glycopeptides

Gentian Violets

Poultry antivirals

Phenylbutazone

### Drugs prohibited from use in any food-producing animals:

**DES – Diethylstibestrol** *(carcinogen)*

**Chloramphenicol** (*non dose dependent aplastic anemia)*

**Nitroimidazoles** *(carcinogens and mutagens)*

* metronidazole
* dimetridazole[[2]](#footnote-2)

**Nitrofurans** including topical (*carcinogens, mutagens, cardiomyopathies)* [[3]](#footnote-3)

* nitrofurazone
* furazolidone

**Clenbuterol**[[4]](#endnote-1) *(concentrated in liver Exerts pharmacological effect)*

**Dipyrone (metamizole)** *(Dipyrone is rapidly metabolized and excreted – not a residue problem. As an old drug its use had been grandfathered in. But when Banamine, a labeled alternative, became available FDA withdrew approval. This was the first instance of FDA making this type of decision on market considerations. If there was sufficient demand a pharmaceutical company could theoretically submit a new drug application).*

**Glycopeptides** e.g.Vancomycin *(resistance concerns)*

**Gentian Violet**[[5]](#footnote-4)

Antiviral compounds in poultry (including adamantane and neuraminidase inhibitors) *(resistance concerns)*

Phenylbutazone in adult dairy cattle[[6]](#footnote-5) *(Flunixin megulamine is a labeled alternative)*

### Drugs prohibited from extralabel use in food-producing animals:

Sulfonamides in adult dairy cattle[[7]](#footnote-6) *(carcinogen)*
Fluoroquinolones[[8]](#footnote-7) *(concerns over development of drug resistance*)
Medicated feeds (*concerns over development of drug resistance)*

**No extralabel use**

Sulfonamides in adult dairy

Fluoroquinolones

Medicated Feeds

# Minor Use, Minor Species Act, 2004 (MUMS)

**MUMS**

Conditonal Approval

Indexed drugs

Orphan Drugs (Designated Drugs)

(e.g. CIDR-g in sheep, florfenicol in sheep, lincomycin

 for foul brood in bees, erythromycin in salmon)

Conditional Approval: Under MUMS, the sponsor of a veterinary drug can ask CVM for “conditional approval,” which allows the sponsor to make the drug available before collecting all necessary effectiveness data, but after proving the drug is safe. The drug sponsor can keep the product on the market for up to five years, through annual renewals, while collecting the required effectiveness data.

Indexing: In some cases, the potential market for a minor species drug is just too small to ever support the costs of the drug approval process, even under a conditional approval. In such cases, FDA now may add the drug to an index of legally marketed unapproved new animal drugs. This provision will be especially helpful to veterinarians treating zoo or endangered animals or classes of animals that include several different species, such as ornamental fish.

Orphan Drugs aka Designated New Animal Drugs: This aspect of the legislation is similar to the “Orphan Drug Act” for humans, which helps pharmaceutical firms develop drugs for limited human uses. It provides incentives for approval. Grants to support safety and effectiveness testing will be available. Companies who gain approval for designated new animal drugs will be granted seven years of marketing exclusivity, which means the sponsor will face no competition in the marketplace for that use of the drug for that time.

## Miscellaneous

Aside from the above AMDUCA list, regulations related to the Pasteurized Milk Ordinance (PMO) prohibit the presence of dimethyl sulfoxide (DMSO) and colloidal silver on dairies.

## Tests for antibiotic residues

A number of tests have been developed for detecting antibiotics in milk at or above the FDA determined safe or tolerant level. For penicillin, for instance, this is 10 ppb.

Milk is picked up from farms by a milk tanker that may call at a number of farms before taking milk back to the processing plant. The driver takes a check sample at each farm. Every tanker load is tested for β-lactams before it is unloaded at the plant. If the load has a violative level then the check samples are use to find identify the farm.

If there is a violative residue the tanker load of milk is dumped, the farmer pays for the whole tanker load, and may lose his permit to ship Grade A milk.

Many farms have test kits on the farm for use if they suspect a mistake has been made, and milk from an antibiotic treated cow has found its way into the bulk tank.

Antibiotic Residue Test Kits

1. farm use
	* Delvotest
	* SNAP tests e.g SNAP β-lactam
	* Charm (various test available)
	* Laktek
	* Penzyme
2. processing plant use
	* most plants use one of the Charm tests

# Industry driven programs to avoid drug residues in meat and milk.

Most food animal industries have their own quality assurance programs. Dairy and swine programs are aimed particularly at avoiding antibiotic residues. Beef cattle programs are also aimed at injection site blemishes and other carcass quality issues (e.g. bruising). These are producer education and certification programs. They are popularly known as “10-Point Programs.”

## Examples of Quality Assurance Programs

**Milk and Dairy Beef Residue Prevention Protocol**

1. Practice Healthy Herd Management
2. Establish a Valid VCPR
3. Use Only FDA Approved OTC or Prescription Drugs
4. Label Correctly
5. Store Drugs Correctly
6. Administer Drugs Correctly and Identify Treated Animals
7. Maintain Treatment Records
8. Use Drug Residue Screening Tests
9. Implement Employee/Family Awareness
10. Complete Protocol Annually

### Injectable Animal Health Products in Beef Cattle

* Products labeled for subcutaneous (SQ) administration should be administered SQ in the neck region (ahead of the shoulders).
* All products labeled for intra-muscular (IM) use shall be given in the neck region only (no exceptions, regardless of age).
* All products cause tissue damage when injected IM. Therefore all IM use should be avoided if possible.
* Products cleared for SQ, IV or oral administration are recommended.
* Products with low dosage rates are recommended and proper spacing should be followed.
* No more than 10 cc of product is administered per IM injection site.

From the Beef Quality Assurance website <http://www.bqa.org/>

**Beef Cattle processing and Treatment Records**

* Following all FDA/USDA/EPA guidelines for product(s) utilized.
* All products are to be used per label directions.
* Extra-label drug use shall be kept to a minimum, and used only when prescribed by a veterinarian working under a valid Veterinary Client Patient Relationship (VCPR).
* Strict adherence to extended withdrawal periods (as determined by the veterinarian within the context of a valid VCPR) shall be employed.
* Treatment records will be maintained with the following recorded:
	+ Individual animal or group identification.
	+ Date treated.
	+ Product administrated and manufacturer's lot/serial number.
	+ Dosage used.
	+ Route and location of administration.
	+ Earliest date animal will have cleared withdrawal period.

When cattle are processed as a group, all cattle within the group shall be identified as such, and the following information recorded:

* Group or lot identification.
* Date treated.
* Product administered and manufacturer's lot/serial number.
* Dosage used.
* Route and location of administration.
* Earliest date animals will have cleared withdrawal period.

All cattle shipped to slaughter will be checked by appropriate personnel to assure that animals that have been treated meet or exceed label or prescription withdrawal times for all animal health products administered.

All processing and treatment records should be transferred with the cattle to next production level. Prospective buyers must be informed of any cattle that have not met withdrawal times.

Footnotes:

1. Quantifying potential human health impacts of animal antibiotic use: enrofloxacin and macrolides in chickens, Coc LA, Popken DA [*Risk Anal*. 2006 Feb;26(1):135-46](http://www.ncbi.nlm.nih.gov/pubmed/16492187). This study draws on existing human health data to predict that ending use of the fluoroquinolone enrofloxacin (which FDA mandated in 2005) and macrolides in U.S. broiler production would be expected to cause an added 1,000 cases of *Campylobacter*-related illness for every one case it avoided by preventing antibiotic resistance. [↑](#footnote-ref-1)
2. Dimetridazole was the only drug available for treating genital trichomoniasis in cattle [↑](#footnote-ref-2)
3. Ointments and puffers ( e.g.NFZ topical powder, Topazone Furazolidone aerosol) are labeled for use in horses. Their prohibition in food animals is based on the fact that although blood levels fall rapidly, some metabolites are more or less permanently bound. [↑](#footnote-ref-3)
4. **Clenbuterol** is a beta-2 adrenergic agonist drug with some anabolic effects. It appears to redirect metabolism from fat to muscle. The drug is approved for veterinary use as a bronchodilator in horses. In

humans, it is used as a weight loss drug. When the drug is used in animals and humans ingest liver or muscle containing the drug, they may experience an increase in heart rate, nervousness, headache,

muscular tremor, dizziness, nausea, vomiting, fever, and chills, typically resolving within 2 to 6 days. As a result of such consequences in humans, the United States and Europe actively monitor urine and tissue samples from livestock for the presence of clenbuterol. It is also being monitored in human athletes at

competitions and competitive games. *(Source PRO-MED 06/22/10)*

**Confirmed outbreak of poisoning by clenbuterol**

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The Jalisco Health Secretariat (SSJ) confirmed today [22 Jun 2010] that 11 people at a party in the municipality of Arandas were victims of poisoning by clenbuterol, bringing the total to 22 affected this

year [2010] by eating meat contaminated with the anti-catabolic agent.

The number of cases has exceeded last year's [2009] total of clenbuterol poisoning cases, which was 17.

Regarding the new cases, the public health director of SSJ, Jose Mario Amezcua Marquez, said the 11 people were at a party in the community of Santiago de Velazquez, Arandas, where they ate meat. All of them had malaise and tachycardia, 9 of them had fine tremors, and half of them suffered headaches and other symptoms. Most of the affected were between 25 and 44 years old, although 1 was less than 24 years old. No children less than 15 were affected. The affected were 7 women and 4 men who did not require hospitalization and are out of danger.

For his part, the Director of Health Regulation, Juan Carlos Olivares Galvez, reported that 11 percent of meat samples tested this year [2010] have tested positive for clenbuterol, which represents an increase of 6 percent from last year's [2009] data.

*(Source PROMED 06/22/10)* [↑](#endnote-ref-1)
5. Gentian Violet was added to poultry feed as a mold inhibitor, but was never approved by FDA. Its use would be extralabel, but there is no extralabel privilege for feed additive drugs. Recently topical gentian violet products have appeared on the market and FDA has re-iterated its ban. [↑](#footnote-ref-4)
6. Although phenylbutazone is only specifically banned in adult dairy cattle its use in any food animal is strongly discouraged. Lactating (adult) dairy cattle are defined by FDA as dairy cattle 20 months of age or older regardless of whether they are milking or dry. [↑](#footnote-ref-5)
7. Currently the only sulfonamide available for use in dairy cattle older than 20 months of age is sulfadimethoxine (Albon). In adult dairy cattle this drug may only be used on-label. Administering higher doses or sustained release sulfadimethoxine products is prohibited. [↑](#footnote-ref-6)
8. Baytril 100 and A-180 are labeled for use in cattle but no extralabel use is permitted [↑](#footnote-ref-7)