HHS:PHS:FDA:CFSAN:OC:DCP:MSB

5100 Paint Branch Parkway
College Park, MD 20740-3835

M-I-06-5

April 19, 2006

TO: All Regional Food and Drug Directors
Attn: Regional Milk Specialists

FROM: Milk Safety Branch (HFS-626)

SUBJECT: Current Information Addressing Item 15r-Drug and Chemical Control Of The Grade "A" Pasteurized Milk Ordinance

The purpose of this coded memorandum (M-I) is to update previously issued guidance on Item 15r of the Grade "A" Pasteurized Milk Ordinance (PMO) addressing drug labeling, use and storage requirements; inspectional areas; and follow up investigations for positive animal drug residues on Grade "A" dairy operations.

This M-I combines M-I-88-9, M-I-90-9, M-I-90-11, M-I-91-2, M-I-92-10, M-I-92-10 (addendum), M-I-96-5, M-I-97-3, M-I-97-4, M-I-98-4, M-I-97-7, M-I-99-1, M-I-01-3, M-I-02-6, M-I-03-5, M-I-03-10, M-I-04-2, and M-I-04-7. All of the above referenced M-I's are now rescinded and will be identified as "INACTIVE" in the next issued revision of the Index of Memoranda of Information (M-I).

NOTE: LISTING OF DRUGS OR PRODUCT TRADE NAMES DOES NOT IMPLY AN ENDORSEMENT OF THEIR USE IN DAIRY CATTLE.

WHY ARE DRUG LABELING AND STORAGE REQUIREMENTS IMPORTANT?

Residues most often occur on the dairy operation, not later in the milk processing channels. Many residues result from the failure to properly follow label directions; resulting in inadequate milk discard or slaughter withdrawal times. Other common causes of drug residues include the failure to adequately identify treated dairy animals and to keep appropriate treatment records; improper extra-label use (ELU) by a dairy producer; and the failure to milk treated cows last or the use of common milking equipment or vacuum source to milk treated and non-treated dairy animals.

The PMO drug labeling and storage requirements are intended to ensure that the dairy producer has adequate directions for use, including appropriate withdrawal time(s), of a product available every time a drug is administered. These requirements are identified in Item 15r of the PMO.

ITEM 15r. DRUG AND CHEMICAL CONTROL

Cleaners and sanitizers shall be stored in properly identified, dedicated end-use containers.
Animal drugs and drug administration equipment shall be stored in such a way that milk, milking equipment, wash vats and hand sinks are not subject to contamination.
Animal drugs shall be properly labeled and segregated, lactating from non-lactating. Unapproved drugs shall not be used.

PUBLIC HEALTH REASON

Accidental misuse of cleaners or sanitizers can result in adulteration of the milk.
Animal drugs can result in adverse reactions in people sensitive to those residues and can contribute to the development of strains of drug resistant human pathogens.

ADMINISTRATIVE PROCEDURES

This Item is deemed to be satisfied when:

1. Cleaners and sanitizers, used on dairy farms, shall be purchased in containers from the manufacturer or distributor, which properly identify the contents or, if bulk cleaners and sanitizers are transferred from the manufacturer's or distributor's container, that the transfer only occurs into a dedicated end-use container, which is specifically designed and maintained according to the manufacturer's specifications for that specific product. The label on the dedicated end-use container shall include the product name, chemical description, use directions, precautionary and warning statement, first aid instructions, container storage and maintenance instructions and the name and address of the manufacturer or distributor.
2. Equipment used to administer drugs is not cleaned in the wash vats and is stored so as not to contaminate the milk or milk-contact surfaces of equipment.
3. Drugs intended for treatment of non-lactating dairy animals are segregated from those drugs used for lactating animals. Separate shelves in cabinets, refrigerators or other storage facilities satisfy this Item.
4. Drugs shall be properly labeled to include the name and address of the manufacturer or distributor for OTC drugs, or veterinary practitioner dispensing the product for Rx and extra label use drugs.
5. Drug labels shall also include:
    a. Directions for use, and prescribed withholding times;
    b. Cautionary statements, if needed; and
    c. Active ingredient(s) in the drug product.
6. Unapproved and/or improperly labeled drugs are not used to treat dairy animals and are not stored in the milkhouse, milking barn, stable or parlor.
7. Drugs are stored in such a manner that they cannot contaminate the milk or milk product-contact surfaces of the containers, utensils or equipment.

NOTE: Topical antiseptics and wound dressings, unless intended for direct injection into the teat, vaccines and other biologics, and dosage form vitamins and/or mineral products are exempt from labeling and storage requirements, except when it is determined that they are stored in such a manner that they may contaminate the milk or milk product-contact surfaces of containers, utensils or equipment.

WHO IS RESPONSIBLE FOR COMPLYING WITH ITEM 15(r)?

The dairy producer is ultimately responsible for assuring that drugs are properly labeled, stored and used on the dairy operation. The minimum label requirements, cited above, provide inspectional evidence that adequate directions for use of a drug product are available to the dairy producer and, in the case of Rx or ELU drugs, that a veterinarian has prescribed the product. If these labeling requirements are not met, the dairy producer may not have adequate directions for the safe and effective use of the drugs and residues may result.

PMO DAIRY OPERATION INSPECTIONAL AREAS

The proper labeling and storage of drugs on the dairy operation is important to ensuring that the producer has adequate directions for use in hand every time a drug is administered to assist in preventing drug residues. It is important that drugs are stored in areas where they may be reviewed during routine inspections, State ratings and FDA check ratings. Such review provides verification that proper labeling and storage criteria, required under Item 15r of the PMO, are in compliance.

FDA has consistently defined that the inspection of a Grade "A" dairy operation includes the milkhouse, milking barn, stable or parlor, adjacent storage areas, cow yard and cattle housing areas, surroundings, waste disposal areas and the water supply and its distribution system. These areas may include dairy animal maternity areas, animal treatment areas or hospital barns, replacement heifer areas, offices, utility rooms, tool sheds (drug cabinets, refrigerators, etc.) or other areas where drugs, used to treat dairy animals, may be used or stored.

With regard to drug storage, labeling and use, the scope of a dairy operation/inspection extends beyond the milkhouse, milking barn or parlor. FDA believes the following areas are part of the milking operation: any area reasonably expected to contain drugs used to treat lactating cattle, cattle that may soon be placed in or returned to a milking herd, or other cattle intended for milk production (replacement heifers). Private residences and vehicles are not included without the permission of the owner or their authorized agent.

DEFINITIONS

Drug: A drug is defined in section 201(g) of the Federal Food, Drug, and Cosmetic Act (FFD&CA), as amended. For PMO purposes, animal drugs are articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other

animals; and articles (other than food) intended to affect the structure or function of the body of animals.

Label: A display of written, printed or graphic matter upon the immediate container of the article. An example is the immediate container label.

Labeling: All labels and other written, printed, or graphic matter upon any article or any of its containers or wrappers or accompanying such article. The package insert, box or carton are examples of labeling.

NOTE: THE INCLUSION OF A SPECIFIC DRUG OR PRODUCT NAME WITHIN THIS M-I IS FOR CITING AN EXAMPLE OF A DRUG OR PRODUCT AND FOR CLARIFICATION PURPOSES ONLY. IT IS NOT AN ENDORSEMENT OF THAT SPECIFIC DRUG OR PRODUCT BY FDA.

GUIDANCE ON TYPES OF DRUGS, LABELING, USE, AND STORAGE

Basically three (3) classes of drugs are found on dairy operations:

1. Over the counter (OTC) drugs are drugs that can be purchased by the producer without a prescription.

2. Prescription (Rx) drugs are drugs that must be dispensed by or on the order of a licensed veterinarian.

- Veterinary Rx drug labeling bears the legend: "CAUTION: Federal Law restricts this drug to use by or on the order of a licensed veterinarian".
- Human Rx drug labeling bears the legend: "CAUTION: Federal law restricts this drug to use by or on the order of a physician".

3. Drugs, either OTC or Rx that are not used according to their label (used off label); more commonly called extra-label use (ELU).

EXTRA-LABEL USE (ELU)

Extra-label (off label) use occurs when a drug product is used contrary to the manufacturer's label directions. This can occur, for example, when a product is used at a different dosage; by a different route of administration; for a different class of animals; or for a disease condition not specified on the label.

FDA recognizes that not all disease conditions affecting food-producing animals have drugs labeled for use in treatment of that condition. FDA has established parameters whereby veterinarians may prescribe approved drugs in an extra-label manner.

Only a veterinarian may use, prescribe, or label an FDA approved animal or human drug for extra-label purposes. Such ELU of drugs by veterinarians is provided for under

the parameters in the Animal Medicinal Drug Use Clarification Act (AMDUCA) of 1994 and Title 21 Code of Federal Regulations, Part 530 (21 CFR 530).
All ELU drugs must be labeled to comply with AMDUCA and Item 15r of the PMO to include:

1. Name and address of the authorizing veterinarian;
2. Name of the active ingredient(s); (This requirement is met by displaying the drug's common, generic, scientific, or chemical name. Listing of a trade or brand name is not acceptable.)
3. Adequate directions for use;
4. Withholding times for meat and milk, even if zero; and
5. Any necessary cautionary statements.

PROHIBITED DRUGS

Because of human food safety concerns, some drugs may not be used to treat food-producing animals, even in an extra-label manner. These include:

Chloramphenicol;
Clenbuterol;
Diethylstilbestrol (DES);
Dimetridazole;
Ipronidazole;
Other Nitroimidazoles (metronidazole);
Furazolidone, Nitrofurazone, and other Nitrofurans;
Sulfonamide drugs in lactating dairy cattle (female dairy cattle 20 months of age or older), except the approved use of sulfadimethoxine, sulfabromomethazine, and sulfaethoxypyridazine;
Fluoroquinolones;
Glycopeptides;
Phenylbutazone in female dairy cattle 20 months of age or older

SULFONAMIDES

Only the three (3) sulfonamides approved and labeled with directions for use in lactating dairy cattle may be used in female dairy cattle 20 months of age or older. Currently only sulfadimethoxine is marketed for use in lactating dairy cattle. AMDUCA does not allow the ELU (off label) of sulfadimethoxine in lactating cattle such as a sustained release bolus or intramammary infusion of an injectable form.

FLUOROQUINOLONE ANTIBIOTICS

Baytril 100 (enrofloxacin) and A180 (danofloxacin mesylate) Drug Use/Storage:
These products contain fluoroquinolone antibiotics. They are approved to treat bovine respiratory disease (BRD) associated with *Mannheimia* (*Pasteurella) haemolytica*, *Pasteurella multocoida*, and *Haemophilus somnus*. The ELU of fluoroquinolones,

including Baytril 100 and A180 is specifically prohibited in Title 21 Code of Federal Regulations, Part 530.41 (21 CFR 530.41).

Baytril 100 and A180 are specifically prohibited for use in cattle intended for dairy production or calves to be processed for veal. This includes all classes of cattle on a dairy operation, including calves reared as dairy cow replacements, heifers, lactating and non-lactating (dry) cows, and bulls maintained for breeding purposes.

Baytril 100 or A180 may be used to treat BRD only in cattle maintained for beef production, i.e., beef or dairy breed feedlot steers, bulls, and heifers.

The restrictions for the ELU of fluoroquinolones are based on human food safety concerns. These concerns include the increased prevalence of certain pathogens with zoonotic potential, such as Salmonella on dairy operations; the higher level of human-animal contact on dairies; and concerns about meat and milk safety.

Because of these human food safety concerns, fluoroquinolones must not be used to treat cattle intended for dairy production or stored in dairy operation drug cabinets.

NITROFURAN DRUGS, FURAZOLIDONE AND NITROFURAZONE

Currently, there are nitrofuran products in the form of powders, solutions, ointments, salves, sprays, and creams, which are labeled for topical use in horses, dogs, and cats and for intrauterine use in horses. They are marketed as legal products for their intended use(s) in non-food-producing animals. The use or storage on dairy operations of any nitrofuran drug, such as sprays, powders, solutions, ointments, salves, and creams labeled for use in horses, dogs, and cats is a violation of Item 15r of the PMO.

OTHER DRUGS

Regulators are reminded that the following three (3) drugs are either not to be used or not to be stored on dairy operations or fed to lactating dairy cattle because of human food safety concerns:

1. NON-MEDICAL GRADE DIMETHYLSULFOXIDE (DMSO)

Industrial grade DMSO is a by-product of the paper industry and is able to carry some drugs rapidly through the skin and other tissues. There are no FDA approved uses for industrial grade DMSO in man or other animals. There are approvals for medical grade DMSO drug product uses in horses and dogs.

Industrial grade DMSO is widely available for various non-medical uses such as paint remover and other solvent uses. In the past, industrial grade DMSO was often found stored on dairy farms or mixed with other drugs intended for use in dairy animals. Such use may lead to an increased chance of drug residues, off odor and off flavor milk.

FDA considers the use of industrial grade DMSO for any veterinary purposes to be illegal. Industrial grade DMSO is an unapproved new animal drug which is unsafe to use in food-producing animals.

> **NOTE**: There are serious medical conditions that may occur in dairy cattle for which the administration of medical grade DMSO may be a life saving treatment option. It is permissible for veterinarians to use FDA approved medical grade DMSO products under AMDUCA in an extra-label manner to treat food animals. To align the PMO with AMDUCA and legitimate veterinary medical practice, the use of medical grade DMSO to treat life threatening conditions in dairy cattle of all classes is allowable. Under no circumstances should the product be stored on the operation for indiscriminate use by dairy personnel.

The storage of DMSO in any form or the use of industrial grade DMSO in any form on a dairy operation is a violation of Item 15r of the PMO.

2. DIPYRONE (Novine, No Pain, etc.)

Dipyrone is not approved for use in animals. It is not legally manufactured or marketed for use in the US. Dairy producers, veterinarians and consultants should be aware that the use of dipyrone is illegal drug use.

3. COLLOIDAL SILVER

The use of colloidal silver-containing products constitutes a potentially serious public health concern because of the possibility of residues in milk or meat. The consumption of silver by humans may result in argyria, a permanent ashen-gray or blue discoloration of the skin, conjunctiva, and internal organs.
Colloidal silver-containing products have never been approved by the FDA for treatment of animal disease in any animal species. Item 15r of the PMO, Administrative Procedures #6 states that "Unapproved and/or improperly labeled drugs are not used to treat dairy animals and are not stored in the milkhouse, milking barn, stable or parlor."

EXTRA-LABEL vs. PROHIBITED DRUGS

Drugs that are not prohibited but are FDA approved for animal or human use may be extra-labeled by a veterinarian. Some are labeled with “Do not use in lactating animals”, “Do not use in female dairy cattle 20 months of age or older”, or “Not for use in adult dairy cattle.” Examples are Draxxin-Rx (tulathromycin), Micotil-Rx (tilmicosin) and Nuflor-Rx (florfenicol).

LABELS FOR SMALL AND IRREGULARLY SHAPED CONTAINERS

The smallest unit size of a drug that can practically be labeled is required to bear labeling information required within Item 15(r) of the PMO. Labeling the outside of cases or cartons of drugs that can bear a label does not meet the PMO requirements.

The only exceptions to the labeling requirements for individual container labeling pertain to containers (vials, tubes, etc.) that are too small or are shaped in such a manner that they will not accommodate a label bearing all the required labeling information. In these cases, the label issued by the dispensing veterinarian is required to be affixed to the next largest package size.

For example, if a product is too small to be labeled and it is packaged in a multi-vial carton, affixing a label to the carton is acceptable. If a veterinarian does not want to prescribe a carton, then the vials should be placed in a container such as a closable plastic bag and the label affixed to the bag.

Many Rx intra-mammary infusion tubes for lactating and non-lactating cows are used on dairy operations. These tubes are packaged in multiple tube boxes containing 4, 12, 24 or even 144 tubes. The multiple tube containers (box, bucket, etc.) must bear a label with the prescribing veterinarian's name and address.

IDENTIFICATION OF THE DISPENSING OR PRESCRIBING VETERINARIAN'S NAME ON THE LABEL

A veterinarian's name and address is required on all Rx and ELU drug containers. Many clinic labels will list more than one (1) veterinarian's name or only the clinic address. In such cases, the name of the individual who actually dispensed or prescribed the drug must be identified on the label. This is often accomplished by underlining, circling, highlighting or checking the name of the prescribing veterinarian.

USE OF PACKAGE INSERTS

Federal regulations allow drug sponsors to include the necessary use information on drug package inserts. Often the immediate container label will state "see package insert". If the PMO (Item 15r) required drug labeling information is included on the insert and not on the container label then that insert must be readily available in association with the container.

SATISFACTORY LABELING OF DRUG PRODUCTS

All drugs stored on dairy operations intended for use on that operation must bear adequate labeling. Dairy operations that are owned by veterinarians or that have a staff veterinarian are not exempted from properly labeling and storing drugs to comply with the PMO labeling requirements.

The labeling of a shelf, wall or carton (for holding multiple labeled containers) with the PMO labeling information does not satisfy the requirements of Item 15r. In such a case, adequate directions for use will not be in hand at the time the drugs are administered to the dairy animal. This is especially important when multiple people or crews treat dairy animals on a dairy operation.

POSTING OF DRUG USE PROTOCOLS (notebooks, folders, etc.)

FDA encourages any mechanism appropriate to educate the producer and dairy operation employees to strictly follow label directions and veterinarian's instructions. The posting of a treatment protocol may have a positive effect in achieving adherence to label use directions. However, the use of protocols or similar mechanisms does not obviate the need for individual container labeling to ensure that adequate directions for use are present and in hand when the drug is administered to a dairy animal. If this is the only labeling information available for the drugs being used on the dairy operation, it would be considered in violation of Item 15r labeling information requirements.

WHO IS ALLOWED TO LABEL PRODUCTS?

Some veterinarians prefer to write prescriptions for drug distributors to fill and deliver Rx or ELU drugs to dairy operations. The PMO does not specify who is allowed to label a product. Some States have regulations as to who may dispense drugs and who may apply labels. The PMO does not mandate who should dispense a drug or who should affix the necessary label information. For PMO purposes the drugs used and stored on the dairy operation must be properly labeled at all times and are evaluated during an inspection of the dairy operation.

EXPIRED, OUTDATED DRUGS

Expired, outdated drugs are not considered a violation of the PMO. We encourage inspectors to educate dairy producers that expired drugs may not work or may be toxic to the dairy animal. Such products should be discarded appropriately.

EXAMPLES OF DRUGS THAT MAY BE FOUND ON DAIRY OPERATIONS

- Draxxin-Rx (tulathromycin) and Micotil-Rx (tilmicosin) are macrolide drugs in the same drug class as erythromycin and tylosin. They are not approved for lactating dairy animals. Under the provisions of AMDUCA licensed veterinarians may extra-label Draxxin or Micotil for use in lactating dairy animals.

- Nuflor® Injectable Solution contains the new animal drug florfenicol. Florfenicol belongs to the same antibiotic family as chloramphenicol. Florfenicol is chemically different from chloramphenicol and is not linked to chloramphenicol's human toxicity concerns (bone marrow suppression and aplastic anemia in humans). The FDA prohibited the use of chloramphenicol in all food-producing animals in 1984.

  Florfenicol, the active ingredient in Nuflor, is not related to the fluoroquinolone class of antibiotics. FDA prohibits the ELU of fluoroquinolones in food-producing animals.

The labeling for Nuflor bears the prescription (Rx) legend. Nuflor is intended for treatment of bovine (cattle) bacterial respiratory disease (pneumonia/shipping fever). Nuflor is labeled for use in all classes of cattle, except female dairy cattle 20 months of age or older and veal calves.

The product has a 28 day meat withdrawal period from the last treatment. A tolerance of 3.7 ppm for the marker residue, florfenicol amine, has been established in cattle liver. The FDA has not established a milk discard time, tolerance or safe level for florfenicol in milk.

Currently, there are no prohibitions under AMDUCA on veterinarians prescribing Nuflor for use in lactating dairy cattle. If prescribed for ELU or if found on the lactating drug shelf on dairy operations, the product must bear an extra-label by a licensed veterinarian that complies with the labeling information requirements of Item 15r of the PMO.

If Nuflor is found on dairy operations stored on the non-lactating shelf, it must be labeled with the prescribing veterinarian's name and address.

The drug sponsor provided FDA with information prior to approval regarding the interaction of the product with some milk screening tests.

For purposes of screening milk under the PMO, the FDA accepted the Charm II milk screening test for the detection of chloramphenicol in raw bovine milk at a 1 ppb level of detection (M-I-92-11) on November 20, 1992. FDA considers any level of chloramphenicol in milk or meat to be violative and a threat to public health.

The Charm II chloramphenicol test is (according to the test kit sponsor) reportedly capable of detecting residues of florfenicol in milk at 25 ppb. Data have not been submitted to the FDA by the test kit sponsor in support of this test for detecting florfenicol residues in milk.

If levels of florfenicol are present in milk in high enough concentrations to result in a positive result on the official Charm II Chloramphenicol test, that milk is considered to be violative under the provisions of the PMO. Any residue of florfenicol in milk indicates the drug was used in an extra-label manner. The AMDUCA does not allow for any levels of florfenicol in milk because no safe or tolerance level has been established. Any positive screening test result conducted by the industry must be reported to the State Regulatory Agency for follow up. The FDA Denver Veterinary Analytical Laboratory can confirm the presence of chloramphenicol residues in milk at 1 ppb.

- RUMENSIN®:

  On October 28, 2004, FDA approved the feeding of Rumensin® (monensin sodium) for increased milk production efficiency in dairy animals. The use of Rumensin in lactating dairy animals constitutes a legal use if the drug is used according to its approved labeling in or top dressed on feed.

  The ELU of other ionophore drugs such as lasalocid in or on animal feeds is not permitted under AMDUCA.

  > **NOTE**: There is no restriction under AMDUCA to prohibit veterinarians from individually dosing sick cows with Rumensin administered in gelatin boluses, as a drench or by stomach tube to treat diseases such as ketosis. This is sick cow treatment and not herd or group prevention.

  FDA has concluded that the meat and milk derived from dairy cattle fed monensin are safe when the dairy cattle are fed according to the approved labeling. In a residue depletion study where dairy cows were given radiolabeled monensin at 1.5 times the intended dose, monensin in milk peaked at approximately 50 ppb, well below the safe concentration of 200 ppb for milk, which supported the assignment of a zero milk discard. Residue information in edible tissues from treated dairy cows confirmed the applicability of the zero withdrawal period already established for monensin in beef cattle. Since monensin is extensively metabolized, it was impractical to develop a regulatory method and FDA waived this requirement. The determinative HPLC method, used to support the original approval of monensin in beef cattle, is available from the Center for Veterinary Medicine (CVM). A tolerance for monensin in milk is not required.

DRUGS EXEMPT FROM PMO LABELING BUT NOT STORAGE REQUIREMENTS

TOPICAL ANTISEPTICS AND WOUND DRESSINGS

The only exempted topical drugs are topical antiseptics and wound dressings. Drugs that are applied topically for a systemic effect are not included in the Item 15r NOTE: exemption cited above. Topically applied drugs that are not antiseptics or wound dressings must comply with all labeling, use, and storage requirements of the PMO.

This category includes creams, salves, ointments, sprays, wound dressings, some foot products, teat dips, tincture of iodine and others. The following is a list of commonly used topical antiseptics and wound dressings that are exempt from the labeling requirements of the PMO. They should only be used topically and must be stored so as not to contaminate the milk or milk product contact surfaces.

Iodine
Alcohol
Hydrogen peroxide (H_2O_2)
Teat dips
Udder washes
Chlorine bleach
Formalin (for cattle foot baths)
Blue Coat
Granulex Spray
Trypzyme Aerosol
Kopertox
Chlorhexidine (Nolvasan) solutions, ointments, and creams for topical use only

SYSTEMICALLY ACTING DRUGS THAT ARE APPLIED TOPICALLY

Any drug stored or used on a dairy operation that is capable of acting systemically and causing residues, which is specifically not approved by FDA regardless of the route of administration, is considered a violation of Item 15r of the PMO.

The following drugs are applied topically for their systemic effect against internal parasites or cattle grubs. They are not topical antiseptics or wound dressings and they are not labeled for use in lactating dairy cattle and; therefore, they are not exempt under the Item 15r NOTE.

DRUG	**TRADE NAME (EXAMPLES)**
Fenthion	Spotton Cattle Insecticide Tiguvon Pour On
Famphur and Xylene	Purina Grub Kill Warbex Famphur Pour On
Phosmet	Star Bar GX-118 Prolate 1-E
Ivermectins and Avermectins	Ivomec Pour On – Doramectin Pour On
Levamisole	Tramisol Pour On Totalon

Because of their potential to cause residues in milk, the use of these drugs on lactating dairy cattle or their storage with the lactating cattle drugs is a violation of Item 15r.

DOSAGE FORM VITAMIN AND/OR MINERAL PRODUCTS

Some of the products in this category are labeled and marketed as Rx or OTC and may have species other than cattle on the label. They are exempt under the labeling requirements of Item 15r of the PMO as dosage form vitamins and/or minerals unless it is determined that they are stored in such a manner that they may contaminate the milk or milk product surfaces of containers or utensils. The following is a list of such products that are commonly used and stored on dairy operations:

Calcium products (injectable or oral use)
Calcium and Dextrose products
Calcium in combination with other minerals such as Magnesium, Potassium, and/or Phosphorus
Dextrose alone or in combination with other minerals
Lactated Ringers
Sodium Chloride
Sterile Water
Potassium Chloride alone or in combination with other Minerals or Dextrose
Electrolytes (oral or injectable use)
Vitamins A and D
Vitamin E and Selenium combinations
Vitamin E
Vitamin B Complex
Vitamin B1 (Thiamine)
Vitamin B12 (Cyanocobalamin)
Vitamin B6 (Pyridoxine)
Vitamin B2 (Riboflavin)
Vitamin C
Vitamin K
Selenium compounds (oral use)
Choline
Pantothenic Acid
Folicin (Folic Acid, and Pteroylglutamic Acid)
Copper containing compounds (injection or oral use)
Iron containing compounds (injection or oral use)
Propylene Glycol
Bicarbonate (injectable and oral formulations)

POLICY ON PROSTAGLANDINS AND PITUITARY HORMONES

Prostaglandins commonly found on dairy operations include:

Cloprosternol (Estrumate)
Dinoprost (Lutalyse)

Pituitary hormones commonly found on dairy operations include:

Oxytocin
Luteinizing Hormones (P.L.H.)
Chorionic Gonadotropin (CG, HCG)
Coricotropin (ACTH)
Follicle Stimulating Hormones (FSH LH)

These products for veterinary use are veterinary Rx drugs. Item 15r of the PMO requires the name and address of the prescribing veterinarian for Rx drugs found on dairy operations.

It is FDA's position that use of these drugs in lactating dairy cattle does not pose human food safety concerns regarding drug residues in milk when used in accordance with label directions.

FDA's position is that the debit for labeling of Item 15r on State ratings or FDA check ratings shall be for those veterinary products for which there is a human food safety concern over the possibility of a drug residue in milk.

Labeling deficiencies of prostaglandins and pituitary hormones shall not be debited when found during the course of State ratings and FDA check ratings.

If information becomes available that raises any concern about these drugs causing residue in milk, we will immediately review this policy.

OVARIAN HORMONES AND ADRENAL HORMONES

Ovarian (estrogens and progesterone) and adrenalin (epinephrine) hormones are not exempted from the PMO drug labeling and storage requirements. Products may contain estrogen compounds such as ECP (estradiol cypionate). Such products may bear an Rx legend. None have ever been approved by FDA for use in animals. ECP is no longer marketed in the US. It should not be used or stored on dairy operations.

Progesterone is sometimes used for reproductive diseases in cattle. Such products are Rx and must comply with Item 15r of the PMO.

Epinephrine is a hormone from the adrenal glands, which is often used to treat shock in animals. Usually full strength epinephrine is labeled as an Rx drug. There are less concentrated OTC formulations. Such products should be properly labeled or extra-labeled by a veterinarian.

MEDICATED AND NON-MEDICATED CATTLE FEED AND BLOCKS

Some cattle feeds and blocks contain drugs. They are identified as medicated feeds or blocks and as such must be labeled and stored properly. One common reason for drug

residues occurring is mistakenly feeding a medicated feed or block intended for use in calves or replacement heifers to the lactating herd. All medicated feeds or blocks should be segregated from non-medicated feeds or blocks.

Medicated feeds or blocks intended for non-lactating dairy animals must be stored inaccessible to lactating dairy animals.

Feed or feed blocks may not contain drugs or other feed additives not specifically labeled for that use. The ELU regulations do not permit anyone to mix drugs in feed in an extra-label manner.

Products labeled as food (feed) unless it is a medicated feed or block are exempt from the drug labeling requirements. Products in this category include but are not limited to:

Non-medicated cattle blocks containing molasses, salt, trace minerals, and vitamins
Products that contain yeast or lactobacillus organisms (direct fed microbial products/ probiotics)

MISCELLANEOUS DRUGS

Examples of such drugs include: Aloe Vera; Homeopathic Drugs; Drugs that are packaged for infusion (intramammary) or injection but labeled for oral (feed), topical, or other routes of administration; and Drugs used in foot baths and sprays for application to dairy animal's feet.

The PMO states that unapproved and/or improperly labeled drugs are not used to treat dairy animals and are not stored in the milkhouse, milking barn, stable or parlor. The PMO further requires that all drugs be properly labeled and that drugs intended for the treatment of lactating dairy animals are segregated from those drugs to be used on non-lactating dairy animals.

1. ALOE VERA

FDA has received complaints of aloe vera being promoted for use as a treatment for mastitis, a cure for high somatic cell counts, as an aid for increasing milk production, and treatment for calf diarrhea. FDA is aware that firms are selling containers of aloe vera with no drug claims on the label to dairy producers and then providing the drug use claims either orally or by other printed materials or graphics (labeling).

No aloe vera product has been approved for the treatment of these serious disease conditions or to increase milk production. Aloe vera products for animals bearing these types of claims are unapproved new animal drugs. Aloe vera products intended for animal use that do not bear adequate directions for animal use are misbranded. The use of unapproved drugs is considered a violation of Item 15r of the PMO.

2. **HOMEOPATHIC DRUGS**

Homeopathy is an alternative therapeutic modality developed in the late 1700's by a German physician for use in humans. Homeopathic medicine is considered an unconventional form of veterinary practice. FDA can find no justification for regulating veterinary homeopathic drugs any differently from other drugs subject to the FFD&CA. There are currently no FDA approved homeopathic drugs for veterinary use.

Homeopathic drugs found on dairy operations must comply with the drug labeling and storage requirements of Item 15r of the PMO. If these do not comply with the drug labeling requirements, they are addressed like other unapproved drugs, and should not be stored on dairy operations or used to treat dairy animals. If homeopathic drugs are properly labeled they are subject to the same storage requirements as any other drug.

> **NOTE:** A thorough reading of the label for homeopathic drugs will often disclose Item 15r deficiencies.

3. **DRUGS PACKAGED FOR INJECTION OR UDDER INFUSION BUT LABELED FOR ORAL OR TOPICAL USE**

FDA has received several complaints about products labeled for oral, topical or other routes of administration that are packaged in a manner customarily considered to be for parenteral (injection and udder infusion) administration. Among the products packaged in this manner are aloe vera products labeled for topical use and packaged in sur-jets/squeeze jets (squeeze tubes routinely used for intramammary infusion); and probiotic and whey blend products labeled for oral use packaged in syringes with sterile diluent in vials with udder infusion cannulas and alcohol pads or packaged in sterile vials closed with a metal ring and rubber injection stopper.

FDA's Compliance Policy Guide (CPG) 7125.39 entitled "Drugs Packaged for Infusion or Injection for Food-Producing Animals" is available for guidance on this issue.

FDA is very concerned about the safety of products not approved for parenteral use which are infused or injected into food-producing animals. FDA believes that the packaging and labeling of these products is a subterfuge to avoid the more stringent regulatory requirements for parenteral drugs. Products that are intended for oral or topical administration should not be packaged to facilitate parenteral (injection and udder infusion) administration. Such drugs will be considered to be misbranded if they do not contain directions for their packaged use.

4. **MEDICATED FOOT BATHS AND SPRAYS USED TO TREAT AND CONTROL CATTLE FOOT ROT AND HEEL WARTS**

Veterinarians prescribe and dairy producers routinely use medicated foot baths or sprays to control hoof disorders in dairy animals. These baths and sprays often contain antibiotics, such as oxytetracycline. To comply with the PMO, these types of baths and

sprays must be operated in a manner that will not contaminate the milk or milk product contact surface of the milking equipment. The use of antibiotics for foot baths/sprays constitutes ELU. Veterinarians should comply with the labeling requirements for ELU of drugs under Item 15r of the PMO.

To prevent milk contamination, foot baths generally should be located on the exit side of the milking area (walk through after milking). Spraying medication onto the dairy animal's hooves should not occur in the milking area during milking time.

TYPES OF DRUGS PRIMARILY REGULATED BY OTHER FEDERAL AND STATE AGENCIES

PESTICIDES/RODENTICIDES; INSECTICIDE SPRAYS, DUSTS, POWDERS AND POUR-ONS

Pesticides/rodenticides/insecticides are registered and regulated by the Environmental Protection Agency (EPA). Ordinarily, an EPA regulated product can be identified by an EPA registration number on the label. Only products labeled for use on or around dairy animals or milking equipment should be used and then only according to their labels. EPA regulated pesticides/rodenticides/insecticides are used only in accordance with the manufacturer's label directions and are used so as to prevent the contamination of milk, milk containers, utensils and equipment, feed and water. Using unapproved pesticides/rodenticides/insecticides or not in accordance with their label directions is considered a violation of Item 19r-Insect and Rodent Control of the PMO and would not be debited under Item 15r of the PMO.

VACCINES AND OTHER BIOLOGICS

Certain drugs are regulated as biologics under the Virus, Serum and Toxin Act (VST Act) administered by the United States Department of Agriculture (USDA) Animal and Plant Health Inspection Service (APHIS). The VST Act prohibits the production for sale or interstate movement of worthless, contaminated, dangerous or harmful biologics intended for use in the prevention, diagnosis, or treatment of animal diseases. Ordinarily, a biologic can be identified by the USDA License Number on the label. Vaccines and biologics are exempt from the drug labeling requirements of Item 15r of the PMO. In general, biologics can be classified as one of the following:

Antigens
Vaccines
Bacterins
Toxoids
Antitioxins

> **NOTE:** Some biologics contain antibiotics as preservatives. The antibiotics are added to biologic products in accordance with 9 CFR 114.10. The concentrations of

antibiotics used in the biologics are well below the levels that are capable of producing an illegal residue in meat, milk or eggs.

DAIRY OPERATION FOLLOW-UP DRUG RESIDUE INVESTIGATION QUESTIONS

With the passage of Proposal 151 at the 2003 National Conference on Interstate Milk Shipments (NCIMS) held April 26 to May 1, 2003 in Seattle, WA, FDA agreed to issue an M-I providing techniques/recommendations on how to conduct an on-dairy operation follow-up investigation to determine the cause of a drug residue in milk. This information was originally issued in M-I-04-2 and is now provided in this M-I to assist State Regulatory Agencies in what areas to check for causes of milk residues. It is not a check list of requirements, which must be completed, prior to the reinstatement of a permit following a confirmed drug residue in milk.

1. Does the dairy producer know or have a suspicion of how the milk was contaminated?

2. Does the dairy producer have a protocol in place to prevent contaminated milk from being shipped?

   If so, describe the protocol utilized by the dairy producer:
   - A. How are treated cows identified?
   - B. How are treated cows segregated and what method(s) is used?
   - C. Describe how the milk is handled from treated cows?
     - 1.) How is contaminated milk collected?
     - 2.) Do they use separate equipment?
     - 3.) What is their source of vacuum for the milking equipment?
     - 4.) Do they milk treated cows last?
     - 5.) How is contaminated milk stored?
     - 6.) Where is contaminated milk stored?
     - 7.) What method(s) is used to dispose of contaminated milk?
   - D. Are dairy operation employees trained regarding the drug residue protocol and the handling of treated cows?
   - E. Has a failure in the protocol been identified?

3. Since the positive drug residue incident, has the dairy producer taken steps to prevent any future occurrences? If so, what steps were taken and was the protocol changed as a result?

4. Review the drug treatment protocol with the dairy producer, at the dairy operation:
   - A. Is drug treatment documentation in order?
   - B. Is the treatment history complete and well documented?
   - C. Is treatment being done under the supervision of a veterinarian? Check the name of the veterinarian and vet clinic.

D. Are the drug storage cabinet and/or area in order and does it correspond to the protocol?
E. Can the dairy producer verify the sources of the drugs in the drug storage cabinet and/or area?
F. If a suspected drug is present, does the dairy producer have proper labeling and use instructions for this drug?
G. Does the dairy producer understand the condition for which the drug has been prescribed?
H. Are the dairy producer and the dairy operation employees aware of milk withholding and discard times?
I. Is the identity of the person administering the drugs documented?
J. Does the dairy producer use management practices to help prevent milk from treated animals from being shipped?
K. Does the dairy producer conduct any drug testing at the dairy operation? (If yes, list the test kit(s) used; does the individual(s) performing the test know how to use the test kit(s); and do they know whom to notify of a positive result.)
L. Does the dairy producer take advantage of any drug testing by the buyer of the milk?

5. Does the dairy producer have a history of shipping drug positive milk? (If yes, list the cause(s) of the repeat occurrences and list what is being done and/or not being done to eliminate repeat occurrences.)

6. Review the findings with the dairy producer. Indicate any shortcomings of any drug testing that is being conducted. As necessary, suggest practices that would help prevent another incident.

7. After the interviewer has discussed all of the above items with the dairy producer, has the dairy producer demonstrated adequate knowledge of what happened and has or is the dairy producer willing to take steps necessary to prevent future incidences?

8. Does the dairy producer require any assistance from the Regulatory Agency to help with the dairy operation’s drug management practices?

NOTE: If specific concerns are identified during this on-site investigation, they should be reported to the State Dairy Program Manager and if warranted they should be forwarded through your FDA Regional Milk Specialist to FDA's Center for Veterinary Medicine (CVM).

An electronic version of this memorandum is available for distribution to Regional Milk Specialists, State Milk Regulatory Agencies and State Rating Officers in your region. The electronic version should be widely distributed to representatives of the dairy industry and other interested parties and will also be available on the FDA Web site at http://www.cfsan.fda.gov at a later date.

If you would like an electronic version of this document prior to it being available on the CFSAN Web Site, please e-mail your request to Robert.Hennes@fda.hhs.gov.

/ss/

Dr. Michael Talley, DVM
Center for Veterinary Medicine

CAPT Robert F. Hennes, RS, MPH, Chief
Milk Safety Branch