Responsible and Legal Drug Use in the Cattle Industry

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Bovine practitioners continue to prove their standing as responsible members of the veterinary profession and as members of the public health community. By putting public health high on your list of priorities, you hold the trust of food safety-conscious consumers. One tangible example of your commitment to promoting public health is demonstrated by avoiding the systemic use of aminoglycosides as well as any use of prohibited drugs in cattle. Another demonstration of your commitment to responsible action is your compliance with the ban on the extra-label use of fluoroquinolones in food-producing animals.

In passing the Animal Medicinal Drug Use Clarification Act, Congress conveyed the public's trust in your ability to use drugs responsibly. In the same light, the Food and Drug Administration (FDA) intends to continue to view veterinarians as partners in protecting public health. It is our intent to develop regulatory enforcement programs which are commensurate with potential risk to public health. The more responsible veterinarians are with regard to on-label and extra-label drug use, the less FDA will need to focus its limited resources on such uses.

Veterinarians can meet these responsibilities by following some established principles.

By following the tenets of the 1994 American Veterinary Medical Association (AVMA) Guidelines for Veterinary Prescription Drugs[1] for both on-label prescription drug use and for extra-label use of drugs.

By adhering to the tenets of the 1994 AVMA Position on Food Safety[2] you are doing your part to assure the quality and safety of food from farm to fork. Among these tenets are:

1. The production of "safe and wholesome" food from healthy animals that are raised in a healthful environment with close professional monitoring to prevent traumatic, infectious, and parasitic diseases and chemical residues.
2. Mandatory animal identification to enable tracking of animals through marketing channels to final products and traceback to origins.
3. Quality assurance programs as cooperative efforts between food animal producers and their veterinarians to meet or exceed standards established by government regulators and expected by consumers.
4. Preharvest certification to comply with production and health standards for food animals should be accomplished by accredited private veterinarians in addition to regulatory veterinarians.
5. Healthful, humane handling of animals throughout production and marketing.

We must, however, remain vigilant to potential threats to the public health. There is rising concern over emerging pathogens that may adversely affect humans. Many of these pathogens are transmitted to humans through animal contact and animal-derived food sources. Also, consumers continue to demand that their food is safe and free of harmful residues. We have a responsibility to diligently apply our medical knowledge to these challenges and, to the extent possible, prevent these public health threats from actually occurring.

Among the new responsibilities for veterinarians is the legal extra-label use of drugs. I would like to describe for you some of the important facets of the new regulations pertaining to extra-label drug use.

Extra-Label Drug Use and the Animal Medicial Drug Use Clarification Act

On October 22,1994, the President signed into law the Animal Medicinal Drug Use Clarification Act of 1994 better known by its abbreviation, AMDUCA. In accordance with the directive from Congress provided in the Act, the Food and Drug Administration (FDA) promulgated regulations to implement the Act. Those regulations became effective on December 9, 1996.[3]

These regulations decriminalize the everyday practice of veterinary medicine and allow veterinarians to prescribe extra-label uses of certain approved animal drugs and approved human drugs for animals. More to the point, it is no longer illegal for a veterinarian to use many of the approved drugs for extra-label use.

AMDUCA establishes conditions for the extra-label use in an animal of any FDA-approved new animal drug or FDA-approved new human drug by or on the order of a licensed veterinarian within the context of a valid veterinarian-client-patient relationship.

A valid **veterinarian-client-patient relationship** is one in which:

1. A veterinarian has assumed the responsibility for making medical judgments regarding the health of (an) animal(s) and the need for medical treatment, and the client (the owner of the animal or animals or other caretaker) has agreed to follow the instructions of the veterinarian;
2. There is sufficient knowledge of the animal(s) by the veterinarian to initiate at least a general or preliminary diagnosis of the medical condition of the animal(s); and
3. The practicing veterinarian is readily available for follow-up in case of adverse reactions or failure of the regimen of therapy. Such a relationship can exist only when the veterinarian has recently seen and is personally acquainted with the keeping and care of the animal(s) by virtue of examination of the animal(s), and/or by medically appropriate and timely visits to the premises where the animal(s) are kept.

Legal extra-label use is limited to treatment modalities when the health of the animal is threatened or suffering or death may result from failure to treat. By removing the word "immediately" which had appeared before the word threatened, FDA clarified that preventive uses are permitted when the health of the animal is threatened.

Quite simply, extra-label use means actual use or intended use of a drug in an animal in a manner not in accordance with the approved labeling. This includes, but is not limited to, uses in species not listed in the labeling, use for indications (disease or other conditions) not listed in the labeling, use at dosage levels, frequencies, or routes of administration other than those stated in the labeling, and deviation from the labeled withdrawal time based on these differences.

An important point to note is that neither AMDUCA nor the implementing regulations are intended to lessen the responsibility of the manufacturer, the veterinarian, or the food producer with regard to violative drug residues or other adverse impact on human health. For example, any amount of residue that may present a risk to the pubic health resulting from an extra-label use would constitute a violation of the Federal Food, Drug, and Cosmetic Act (the Act) subject to enforcement action if a safe level or tolerance has not been established. Residues exceeding an established safe level would also constitute a violation of the Act, as would a residue resulting from an extra-label use where the residue exceeds an established tolerance.

In general terms, AMDUCA codifies into law the provisions for responsible extra-label drug use established in the previous Compliance Policy Guide (CPG). Beyond the provisions of the CPG, AMDUCA includes several safeguards in allowing veterinarians to prescribe drugs for extra-label uses. These provisions are captured in the implementing regulations. Under AMDUCA, there are three "levels of concern" regarding extra-label uses:

1. The FDA may establish a safe level for residues from extra-label use and may require the development of an analytical method for residue detection.
2. In the event that the FDA has reason to believe that a particular extra-label use may present a risk to the public health, the agency may have access to veterinarians' records to estimate the amount of actual extra-label use.
3. The FDA may prohibit extra-label use by order after providing an opportunity for public comment.

Veterinary Records

One of the areas of great concern to practicing veterinarians regarding AMDUCA is that FDA now has legal access to a veterinarian's records. I want to emphasize that the main purpose of record inspection is to ascertain the extent and nature of an extra-label use that FDA has determined may present a risk to the public health. The main purpose of the inspection, therefore, is not enforcement of these regulations. In order for FDA to gain access to a veterinarian's records, FDA must determine that a particular extra-label use may present a risk to the public health. FDA intends to informally announce such findings in CVM Updates and on the CVM Homepage. After the announcement, FDA will determine how best to survey veterinary practices to gather useful information regarding a particular extra-label use. FDA will contact veterinarians in advance of an inspection and set up an appointment. FDA will be requesting very specific information regarding the particular extra-label use:

1. The established name of the drug and its active ingredient
2. The condition treated
3. The species of the treated animal
4. The dosage administered
5. The duration of treatment
6. The numbers of animals treated
7. The specific withdrawal, withholding or discard time for meat, milk and/or eggs.

Veterinarians are required to maintain records of extra-label uses that contain this information for two years or as otherwise requested by State law, whichever is greater. The regulations allow for FDA to have access to the records and allow for the practitioner to copy or reformulate records to provide inspectors with

only information required by the regulations.

Extra-Label Uses Prohibited Under AMDUCA

Under AMDUCA, there are a number of situations in which the extra-label use of a drug would be prohibited. These include:

1. Extra-label use in an animal of an approved animal drug or human drug by a lay person (except when under the supervision of a licensed veterinarian).
2. Extra-label use of an approved new animal drug or human drug in or on an animal feed.
3. Extra-label use resulting in any residue which may present a risk to the public health.
4. Extra-label use resulting in any residue above an established safe level, safe concentration, or tolerance.
5. Extra-label use of a drug when an approved animal drug exists for the intended use and the approved drug has not been determined to be ineffective within the context of a valid veterinarian-client-patient relationship.
6. Extra-label use of any drugs specifically prohibited by regulation.

Prohibition of Extra-Label Uses

AMDUCA gives the FDA authority to prohibit specific extra-label uses in food animals. This Act provides a stepwise procedure leading to a prohibition, however, the FDA need not take all the steps before it prohibits an extra-label use, provided that it makes a finding that the extra-label drug use "presents a risk." An extra-label drug use is permissible until it is prohibited, provided that other parts of the regulation are met.

If the FDA finds that there is a reasonable probability that a particular extra-label drug use may present a risk, it may establish a safe level. If it establishes a safe level, it will publish an order in the **Federal Register**, and codify the safe level. The FDA may also require the development of an analytical method. The FDA will publish a notice of the requirement and an order in the **Federal Register**, and will codify the method.

If the FDA finds that an extra-label drug use may present a risk, it may inspect veterinarians' records. The purpose of the inspection is to ascertain the extent and nature of the extra-label use, not for enforcement purposes. The FDA intends to provide informal public notice when it makes such a finding.

If the FDA finds that an extra-label drug use presents a risk, or a required analytical method has not been developed, the FDA may prohibit the use. If it does so, the FDA will publish an order in the **Federal Register**, with a 90-day delayed effective date and a 60-day comment period. The order will be effective in 90 days, unless revoked or modified, or the comment period is extended. The prohibition will be codified.

A prohibition may be a general ban on the extra-label use of the drug or class, may be limited to a specific species, indication, dosage form, route of administration, or a combination of factors. The regulations have provisions for establishing and announcing safe levels and announcing analytical methods.

Labels

Any human or animal drug prescribed and dispensed for extra-label use by a veterinarian or dispensed by a pharmacist on the order of a veterinarian must bear or be accompanied by labeling information adequate to assure the safe and proper use of the product. This information includes:

1. The name and address of the prescribing veterinarian (If the drug is dispensed by a pharmacy on the order of a veterinarian, the labeling should include the name of the prescribing veterinarian, and the name and address of the dispensing pharmacy.),
2. The established name(s) of the drug(s),
3. Any directions for use specified by the veterinarian, including animal or herd, flock, pen, lot, dosage, frequency, and route of administration, and duration of therapy,
4. Any cautionary statements,
5. The veterinarian's specified withdrawal, withholding, or discard time.

Conditions for Permitted Extra-Label Animal and Human Drug Use in Food-Producing Animals

The following conditions must be met for a permitted extra-label use in food-producing animals of approved new animal and human drugs:

1. There is no approved new animal drug that is labeled for such use and that contains the same active ingredient which is in the required dosage form and concentration, except where a veterinarian finds, within the context of a valid veterinarian-client-patient relationship, that the approved new animal drug is **clinically ineffective** for its intended use.
2. Prior to prescribing or dispensing an approved new animal or human drug for an extra-label use in food animals, the veterinarian must:

i) Make a careful diagnosis and evaluation of the conditions for which the drug is to be used;

ii) Establish a substantially extended withdrawal pe-

riod prior to marketing of milk, meat, eggs, or other edible products supported by appropriate scientific information, if applicable;

iii) Institute procedures to assure that the identity of the treated animal or animals is carefully maintained; and

iv) Take appropriate measures to assure that assigned timeframes for withdrawal are met and no illegal drug residues occur in any food-producing animal subjected to extra-label treatment.

The following additional conditions must be met for a permitted extra-label use in food-producing animals of an approved human drug, or of an animal drug approved only for use in animals not intended for human consumption:

1. Such use must be accomplished in accordance with an appropriate medical rationale; and
2. If scientific information on the human food safety aspect of the use of the drug in food-producing animals is not available, the veterinarian must take appropriate measures to assure that the animal and its food products will not enter the human food supply.

Lastly, it is important to note that the extra-label use of an approved human drug in a food-producing animal is not permitted if an animal drug approved for use in food-producing animals can be used in an extra-label manner for the particular use.

Compounding of Approved New Animal and Approved Human Drugs

FDA has for a number of years actively regulated the distribution of drugs for compounding in veterinary medicine, especially compounding from bulk drugs for use in food animals. We define compounding as any manipulation to produce a dosage form drug other than the manipulation that is provided for in the directions for use on the labeling of an approved drug product. Compounding can be done from an approved or unapproved finished dosage form as well as from a bulk drug substance.

More than 50 veterinary drug distributors and veterinarians were prosecuted during the 1980's and early 1990's for distributing bulk drugs for use in compounding by veterinarians. In addition, two civil actions — the Algon and Schuyler cases[4,5] — led to decisions by appellate courts that the law does not permit veterinarians to compound from bulk drugs. In other words, there is not a "practice of medicine" exception to the statutory requirement that animal drugs ordinarily need an FDA approval. Until the passage of AMDUCA, the law has also been interpreted that any compounding from an approved drug was an illegal extra-label use of the approved drug.

The FDA, nevertheless, recognized that there was a need for compounding in limited circumstances, both from approved and bulk drugs. Thus, we recognized the need to issue guidance explaining how we might exercise our enforcement discretion in the area of compounding. The end result was Compliance Policy Guide 608.400, "Compounding of Drugs for Use in Animal," published in 1996.

The CPG was several years in the making. The policy guidance likely would have been issued sooner had the FDA decided to make animal drugs a part of the CPG that was developed in the early 1990's for compounding of drugs for use in human medicine. However, we decided that the unique circumstances involving animal drugs, especially the concern for human food safety, required publication of a separate document. In addition, we spent considerable time and effort communicating with stakeholder groups before publishing the CPG.

Congress passed AMDUCA as the Center for Veterinary Medicine was nearing completion of the CPG. AMDUCA authorizes compounding from approved drugs, i.e. compounding is an extra-label drug use. The passage of AMDUCA crystallized the need for guidance on compounding from approved products, even though such uses would no longer be made primarily within the context of the exercise of enforcement discretion by the FDA. The AMDUCA regulations include a section 21 CFR 530.13, that establish the broad parameters for compounding from approved drugs.

The CPG provides detailed guidance for compounding from dosage form drugs (approved and unapproved, animal and human) and bulk drugs. It applies to compounding by veterinarians, and by pharmacists on the order of veterinarians. The CPG sets out conditions and criteria for acceptable compounding from approved drugs, and parameters of enforcement discretion for compounding from bulk drugs and unapproved finished dosage form drugs. The CPG delineates very limited circumstances under which compounding from bulk drugs for use in food animals will not ordinarily be subject to regulatory actions.

Any other compounding that raises public health concerns is identified as high priority, as is compounding drugs that are similar to approved drugs, and commercialization of the compounding activity. Lower priorities are identified for compounding, under specified circumstances, for use in non-food animals and minor food animals.

The following summarizes the relationships between AMDUCA and the CPG. The regulations implementing AMDUCA apply only to compounding from approved drugs (both animal and human). Al-

though section 530.13 of the regulation provides general rules for compounding from approved drugs, it is important to be aware that all the other sections of the AMDUCA regulations apply to compounding as well. Because AMDUCA applies only to extra-label use of approved products, the AMDUCA regulations do not apply to compounding from unapproved finished forms or bulk drugs. Such compounding is illegal, but the CPG provides guidance as to the circumstances in which the FDA will exercise its enforcement discretion with regard to compounding from those drugs.

Compounding of approved animal or human drugs is permitted if all of the following conditions are met:

1. There is no approved new animal or approved new human drug that will, in the available dosage form and concentration, appropriately treat the condition diagnosed. Compounding from a human drug for use in food-producing animals will not be permitted if an approved animal drug can be used for the compounding.
2. The compounding is performed by a licensed veterinarian within the scope of a professional practice.
3. Adequate procedures and processes are followed that ensure the safety and effectiveness of the compounded product.
4. The scale of the compounding operation is commensurate with the established need for compounded products (e.g. similar to that of comparable practices).
5. All relevant State laws relating to the compounding of drugs for use in animals are followed.

Sources of Residue Information

In order for the bovine practitioner to assure that no harmful residues occur as a result of a particular extra-label use, a review of the available relevant information is crucial. Fortunately, there are a number of sources of information from which the bovine practitioner can derive useful information.

One of the most complete sources of information is through FARAD, the Food Animal Residue Avoidance Databank. FARAD can be reached by calling 1-888-US-FARAD. E-mail messages may also be sent, but callers must be sure to provide all the needed information in the message. In addition, the Journal of the American Veterinary Medical Association began, in March, an ongoing feature called "FARAD Digest" to assist veterinarians with the implementation of AMDUCA.[6]

Another good source of residue information is the open scientific literature. The ISI/NOAH World Veterinary Index[7] contains over 70,000 references and citations from 85 veterinary medical journals and is the most comprehensive on-line literature database available devoted exclusively to veterinary medical topics. It is available through a subscription to NOAH and will soon be accessible on the AVMA's home page (http://www.avma.org). For more information contact the AVMA Center for Information Management.

Another source of information are the toxicological monographs available from the Joint FAO/WHO Expert Committee on Food Additives (JECFA). The World Health Organization (WHO) and Food and Agricultural Organization (FAO) can be accessed on the Internet at:

http://www.who.org
http://www.fao.org

Also, the United States Pharmacopoeia (USP) produces drug monographs that contain important drug use information. Currently, the USP has monographs on nearly 90 drugs for animal use and can be reached by telephone at *(301) 881-0666.*

Cowside Use of Screening Tests

An important strategy in preventing harmful residues from entering the human food supply is to test the food or the animals from which the food is derived, for the presence of unsafe residues. This long standing practice in the dairy industry has been under intense scrutiny for the last 10 years. As we learn more about the usefulness of tests designed to identify harmful residues, we also learn of their limitations. Recent research at FDA reveals some interesting findings.

The FDA announced in 1993 its interest in developing a protocol for the evaluation of screening tests for milk from individual cows. A number of meetings were held involving representatives of the industry, including the National Mastitis Council. A protocol was designed using the same administrative procedures as for the accepted tests for commingled milk with the test manufacturers paying for the evaluation. Because there is no regulatory requirement for the testing of milk from individual cows, the manufacturers perceive no economic incentive to have their tests evaluated, and consequently, no tests have been evaluated under this protocol.

Recognizing the concerns in the literature for false positive results on milk from individual cows and the importance of having reliable, independently evaluated tests available for use by the producer/practitioner for milk from individual cows, the FDA decided to fund an evaluation of the tests. Recognizing the screening tests which had already been evaluated for commingled milk and the parameters included in that evaluation, FDA developed a different protocol using the selectivity and mastitis concerns as parameters for additional evaluation. This protocol addresses the issues of false positive test results in milk from individual cows which are

healthy and have not been treated with drugs and also a mastitis model to address the issues of cows recovering from mastitis. In the mastitis model study, the tests must provide the correct result on a milk sample from healthy cows and also on visually normal milk following recovery from an endotoxin challenge in the udder. The tests must also respond correctly to the visually normal milk when claimed drugs are added. The Agricultural Research Service at the USDA, Beltsville, MD collaborated with FDA's Center for Veterinary Medicine (CVM) for this study. Nine of the currently accepted tests for commingled milk were evaluated. *The results of this study will be presented this summer, and the full report is forthcoming.* Briefly, the tests performed well when evaluated for false positive test results, however, a number of the tests gave false negative results when the milk was spiked with representative beta-lactams. Obviously, this is troubling in terms of the reliability of the tests for individual cows. We have not seen this problem on commingled milk.

As screening tests can detect drug concentrations below the tolerance/safe level, a positive test result is possible with a screening test on a milk sample collected from cows after the labeled milk discard time. For this reason, CVM does not recommend the use of screening tests on cows which have been individually treated in accordance with label directions. It should be noted, however, that these lower concentrations will not cause a violative or non-violative positive truck tanker except in those exceptional cases where a large percentage of the herd is treated at the same time or a single farm is the only one on the tanker. If it is desirable to have no detectable residue in milk from individual cows, then testing with a screening test until the sample is negative is a viable option. To preclude the possibility of a truck tanker positive result, screening tests may also be used in milk from individual cows treated in an extra-label manner.

A good review of the current thinking regarding drug residue screening methods is published in the proceedings of the 36th Annual Meeting of the National Mastitis Council.[8,9,10,11]

ADAA

Another key piece of legislation that impacts on the availability of drugs for the bovine practitioner is the Animal Drug Availability Act (ADAA). This Act was signed into law on October 9,1996. The purpose of the ADAA is to make changes to the animal drug provisions of the Federal Food, Drug, and Cosmetic Act to facilitate the approval of new animal drugs. The ADAA accomplishes this by building flexibility into the animal drug review processes without decreasing FDA's existing authority to ensure that animal drug products are safe for the animals for which the drug are intended and for the humans who consume animal food products. Congress directed FDA to implement the law and its spirit pending promulgation of implementing regulations.

The ADAA redefines in section 512(d)(3) of the Act, the term "**substantial evidence**," that is, the evidence needed to establish that a new animal drug is effective. Under the Act, FDA may refuse to approve a new animal drug application if it finds that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended or suggested in the proposed labeling.

With the change effected by the ADAA, it is now possible that as few as a single adequate and well-controlled study may provide substantial evidence of the effectiveness of a new animal drug. A field investigation may not be required to support every application. Prior to enactment of the ADAA, the Act required at least one field investigation to be conducted to support a finding that a new animal drug was effective. With the enactment of the ADAA, the decision whether a field investigation is necessary to support a finding that a new animal drug is safe or effective will depend on the nature of the new animal drug and its intended use. Sponsors can discuss with CVM whether a field investigation is necessary during a presubmission conference.

The standard for studies to support a finding that a new animal drug is effective is still the **adequate and well-controlled study**, but CVM will further define the term "adequate and well-controlled" as that term applies to field investigations to require that field investigations be designed and conducted in a scientifically sound manner. The ADAA has directed that FDA publish a proposed regulation to provide such a definition within 6 months of the enactment of the ADAA.

Also, the studies to support a finding that a new animal drug is effective must be conducted by experts qualified by scientific training and experience to evaluate the effectiveness of the new animal drug and it must be concluded by experts qualified by scientific training and experience that the drug will have the effect it is intended to have under the specified conditions of use.

The ADAA creates a new section 512(d)(4) in the Act that describes a streamlined process for the approval of a **combination new animal drug** if each of the animal drugs used in the combination has been previously approved individually for the uses for which it is intended in the combination. CVM intends to develop regulations and guidance to implement this provision.

In accordance with the new section 512(b)(3) of the Act, FDA must grant a **presubmission conference** (PSC) to a sponsor if one is requested. The purpose of the PSC or, more likely presubmission conferences, is

to reach agreement on the requirements for an INAD or NADA submission. Agreement reached during a PSC is binding unless parties agree to modify or FDA substantiates reasons for changing a requirement. It is necessary to be able to modify the PSC agreements because science is by its nature an iterative process and results of studies may lead the sponsor or CVM to conclude that other studies or a different approach is appropriate or more efficient.

Under the ADAA, section 512(d)(1)(F) of the Act relating to the limitation of residues has been modified. CVM is no longer required by the Act to approve a drug at the optimal dose but can approve a dose range. This change will facilitate CVM's flexible labeling initiative. The wider use of dose range labeling will permit veterinarians to exercise greater professional judgment in administering drugs to animals.

Under the ADAA, FDA is now authorized by section 512(A)(6) of the Act, to set **import tolerances** for animal drugs that are not approved in the US but may be present as residues in edible animal products imported into the US.

The ADAA revised section 512(m) of the Act. The result is that feed mills will no longer be required to have multiple Medicated Feed Applications permitting the manufacture of animal feeds bearing or containing certain particular new animal drugs. Instead, a feed mill can obtain a single **feed mill license**.

In addition to revising sections of the Act, the ADAA instructed FDA to do several things, including to announce within 18 months proposed regulatory or statutory changes to facilitate such approvals of animal drugs intended for use in **minor species and for minor uses**.

Veterinary Feed Directive (VFD) Drugs

The ADAA added to the Act a new section 504, **Veterinary Feed Directives** (VFD). This section creates a new class of animal drugs for use in feed similar to prescription animal drugs. VFD drugs are drugs intended for use in or on animal feed which are limited by an approved application to use under the professional supervision of a licensed veterinarian. VFD drugs and animal feeds containing them must be labeled with a cautionary statement and the animal feed containing a VFD drug can only be used by or upon the lawful VFD issued by a licensed veterinarian in the course of the veterinarian's professional practice. FDA intends to propose regulations which will include prescribing the cautionary statement and the content of the VFD records.

The VFD classification of animal drugs provides an alternative solution to designating certain drugs in medicated feed as prescription drugs. Use of prescription antibiotics in animal feeds was previously considered impractical because many state pharmacy laws do not distinguish between human and veterinary products and require the dispensing of prescription drugs to be conducted by licensed pharmacists. The VFD allows a simpler process for dispensing medicated feeds to animals, one that requires veterinary involvement but does not require the involvement of a licensed pharmacist.

During the evaluation of a new animal drug application, FDA determines the marketing status (prescription or over-the-counter) of animal drug products based on whether or not it is possible to prepare adequate directions for use under which a lay person can use the drugs safely and effectively. An animal drug which, because of its toxicity or other potential for harmful effects, or method of its use, or the collateral measures necessary for its use, is not safe for animal use except under the professional supervision of a licensed veterinarian is a prescription drug and can be dispensed only by or upon the lawful written order of a licensed veterinarian. Products for which adequate directions for lay use can be written are labeled for over-the-counter use under existing law. If adequate directions cannot be written, the prescription classification provides a method of distribution and control which is intended to ensure that the prescription product reaches only the hands of persons appropriately trained to use the product. Under the supervision of a veterinarian, this can include animal owners or managers.

Just as each label claim for a new animal drug must be approved, so too must the drug be specifically approved for administration in animal feed. Approvals are issued only for the uses, claims and drug levels which have been shown to be safe and effective by adequate and well-controlled studies. The feed must be labeled in accordance with the regulations if sold or delivered to a second party.

Except for one drug approved for use in swine, all commercially available food-animal drugs intended for use in medicated feed are now available on an over-the-counter basis. Animal producers are free to purchase, mix, and feed these products without the involvement of a veterinarian. Certain new therapeutic antimicrobial agents that have been approved for prescription status were unable, until recently, to be used in animal feeds because of the need for greater control over their use. The VFD drug classification offers an alternative to prescription status, allowing veterinarian supervision of these types of drugs while enabling the feed industry to maintain current good manufacturing practices with minimal disruption to feed distribution. All antimicrobial agents for therapeutic use in feed will be approved by FDA in the future as VFD drugs. The participation of a veterinarian in the decision to use one of these drugs satisfies FDA's concerns that the drugs be used only in

appropriate circumstances.

A VFD drug can only be fed to animals in a manner consistent with the FDA conditions of approval. Extra-label use, even if specified by a veterinarian, is not permitted. The labeling, distribution, holding, or use of a VFD drug or feed in a manner inconsistent with its approval results in an adulterated drug or feed.

Many FDA regulations, policies and processes are undergoing development and change and the result of these activities will impact on the future of animal drug availability and use. The bovine practitioner will benefit from these new ways of regulating animal drugs. **Because of the rapid rate of regulatory change, it is important for the bovine practitioner to remain current with new developments.** We, at CVM, are happy to provide you with information and assist you in answering questions regarding FDA regulations and policies. Please feel free to contact us by telephone at *(301) 594-1740* or visit our Homepage at http://www.cvm.fda.gov.

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Abstract

Acute maduramicin toxicity in calves

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A herd of 277 beef-breed calves in three age groups with mistakenly given the poultry coccidiostat maduramicin in a total mixed ration. It caused an acute toxicosis in which sudden death was the sole clinical finding in most cases. One group of 212 calves aged five to eight months suffered a mortality of 51 per cent in eight days and a total mortality of 56 per cent during the 40 days in which mortality was recorded. Mortality of only 3 per cent was recorded in two other groups of calves aged nine to 16 months in eight days and a total mortality of 11 per cent over the 40-day period.