Federal Regulation of Drugs Administered through Feed

George Graber, *Ph.D.*
Director, Division of Animal Feeds
Center for Veterinary Medicine
Food and Drug Administration
Rockville, MD 20857

It is a pleasure for me to be part of this program on nutrition and nutritional diseases in food animals. Although my formal education was in animal nutrition, it has been very difficult to keep up with new advances. In fact, it has been difficult to maintain a working knowledge in amino acid nutrition, an area I spent many years researching. Therefore, I intend to listen attentively to what is said by others from this podium.

I did not accept this speaking engagement for it to serve as a mechanism to propel at you grandiose ideas on drug regulation. Rather, I envisioned my being here more basic; namely, to describe the responsibilities of the Food and Drug Administration (FDA) in regulating drugs in animal feeds. I intend to cover the mandates and definitions created by Congress, the procedures and policies established by FDA to carry out our mandates, and the agency's current position on several topics, including prescription medicated feeds.

The Federal Food, Drug, and Cosmetic Act (hereafter referred to as the Act) is the basic food and drug law in the United States. It is not a new statute, having been enacted in 1906 with significant amendments passed in 1938, 1958, 1962 and 1968. Usually these amendments occurred after some major health disaster; however an exception was the 1968 Animal Drug Amendments whose principal purpose was to locate in one section of the Act (Section 512) the principal provisions which relate to premarket clearance of new animal drugs, either directly or via the animal's feed and water. Up until that time, several sections of the Act were involved in the clearance of new animal drugs, complicating the process which resulted in long delays in drug approval.

In the case of animal drugs, Section 512 of the Act is intended to assure the consumer that they are safe and effective for their intended uses. This is principally accomplished through premarket clearance coupled with surveillance of marketed drugs. In the case of drugs administered directly to the animal, the premarket clearance process involves normally one party, the drug manufacturer. Drugs administered through feed however require a two-tiered premarket clearance process involving first the manufacturer of the drug premix and second the operation that incorporates the drug premix into animal feed (i.e., a feed mill).

Before proceeding with this unique approval process, some mutual understanding of terms should prove helpful. Under the Act, "food" is defined as an article used for food or drink for man or other animals including components of such article. Thus, food covers both human food and animal feed and any nutrient ingredient (e.g., minerals, vitamins and amino acids) which is added to a human food or animal feed is also a food by definition. The Act defines the term "drug" as (A) articles recognized in the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animal; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as components of any articles in (A), (B), or (C).

Label and labeling are two terms quite often confused. Label is defined under the Act as a display of written, printed, or graphic matter upon the immediate container of any regulated article (e.g., food or drug). Labeling on the other hand is more encompassing covering both labels and other written, printed, or graphic matter that accompanies the regulated articles. Thus, brochures for example that are sold with an article must not make representations that are false or misleading.

These definitions on the surface appear straightforward, necessitating little legal interpretation. For example, penicillin is recognized as a drug by name and soybean oil meal is clearly an animal food (feed). We do run into difficulties when statements about the worth of a feed go beyond its nutritional merit. When disease statements are made in labeling, such as when a mineral supplement is represented to aid in the treatment of scours, an animal feed can also be a drug. Under such circumstances, a decision to regulate such a product either as a drug or food is needed. It is our current policy that non-medicated animal feeds are not in violation of the Act provided, among other things, that their labeling does not contain any statement which represents or suggests a therapeutic purpose for its nutritional ingredients. A literal reading of the Act would dictate that a food purported to prevent a nutritional disease could be regulated also as a drug. From a practical viewpoint there is essentially no difference in the effect of an article labeled as a supplemental source of nutrients (i.e., one which has traditionally been regulated as a food) and one labeled for the prevention of a nutrient deficiency or of a deficiency disease which would be

solely and directly the result of inadequate intake of the nutrient. Thus, feed products labeled for prevention of a nutritional disease are usually regulated as food by FDA. Food labeled to treat a disease, nutritional or otherwise, will under most situations be regulated as a drug.

Let me digress briefly to complete this scenario by presenting the Center's policy pertaining to nutritional ingredients in animal drug dosage form products (e.g., injectables). When a new animal drug application is required, it will not be approved unless labeling includes a statement that the nutrient is included to prevent and/or treat the dietary deficiency associated with the disease:

(1) When a single claim for the prevention and/or treatment of a disease is made, the nutrient is demonstrated to contribute in an additive manner to the overall efficacy of the label claim.
(2) When a separate claim (such as a prevention and/or treatment of a dietary deficiency) is made for a nutrient ingredient other than that made for the drug component, data (published or unpublished) are provided to show that a dietary deficiency occurs concurrently with the disease in question in a significant portion of the target animal population, and that the drug alone does not alleviate the deficiency.

Let's return now to the two-tiered FDA preclearance process for drug premixes. The new animal drug application generated by the drug's sponsor represents an extensive investment in time and money. It must contain all proposed labeling; a full description of methods, facilities and controls for manufacturing, processing and packing of the drug; a description of methods for determining the quantity of the drug or its metabolites in or on food derived from treated animals; evidence to establish safety and effectiveness; an environmental assessment; a statement that the studies were conducted in compliance with good laboratory practice regulations; and a summary basis of approval under the Act. When the application is approved, a regulation is published in the Federal Register which serves as the basis for approval of subsequent medicated feed applications. The manufacturing facility is required to be registered and inspected once every two years for compliance with appropriate current good manufacturing regulations (21 CFR 226).

The purpose of the medicated feed application (MFA) (FDA-1800) is to show to the agency that the user of the drug premix can adequately manufacture and properly label the medicated feed. Although the MFA is not very extensive, requiring considerably less information than a new animal drug application, it is a legal contract between the medicated feed manufacturer and the FDA and therefore should not be treated lightly. The main components of an MFA are identification of the regulation that provides the basis for approval of the application, a paper demonstration of a working understanding of the regulation and either a copy of the brand or generic label for the medicated feed(s) covered by the application.

Feed mills mixing medicated feeds that are for sale are required to register with FDA as drug manufacturers, whether or not drug premixes requiring an approved MFA are used. On the other hand, producers mixing medicated feeds where an approved MFA is necessary need to register while registration is not necessary if an approved MFA is not required and the feed is intended for the producer's own animals. Feedlots feeding medicated feeds to animals under consignment do not meet the latter criterion and thus are required to register with FDA. Registration brings with it the mandated once-in-every-two-year inspection requirement, which in this case covers compliance with medicated feed good manufacturing practice regulations (21 CFR 225).

As I hinted in the previous paragraph, all drug premixes do not require an approved medicated feed application for their use. Exemptions to the need of an approved MFA have been granted starting with enactment of the 1968 Animal Drug Amendments for a multitude of reasons. Currently, approximately 30 drug premixes can be used without an approved MFA.

Unfortunately, safety wasn't the primary issue in granting these exemptions. For almost seven years, FDA has been trying through the comment and rulemaking process (which is inherent in our legislative system) to rearrange drug premix exemptions such that those drugs with greater concern from a public health aspect would be given higher agency oversight (i.e., MFA's, registrations and inspections) while drugs with a lesser concern would be exempt from the need of a MFA, registration would not be necessary, a less stringent set of GMPs would be in place, and inspection for GMP compliance would not be routine. This is the main thrust of the so-called Second Generation Medicated Feeds Program which some of you have probably heard about. There is considerably more detail to it which time will not permit me to cover today. However, I believe it is accurate to state that publication of this final rule (which we hope to be soon) should increase the arsenal of drug premixes available in your practices. Let me explain.

The distribution of drug premixes for use in the manufacture of medicated feeds, whether for the producer's own use, or for sale, or to a licensed veterinarian is restricted to holders of approved MFAs, unless the premixes are exempted. It is important to understand that MFAs are approved only for persons having the facilities and procedures adequate to manufacture the medicated feed. As indicated above, a handful of premixes are exempted. However, essentially all the remaining drugs are exempt from the MFA requirement at lower concentrations, many of which are not practical for your office use. Under Second Generation, all drugs should be available at what you might classify as premix levels for your use without the need of a MFA (i.e., exempted).

There are important considerations in using drugs. If the use of a drug premix, or for that matter any drug product, by a veterinarian results in violative residues in edible animal

products, the veterinarian may be held liable. FDA's policy has always been to hold responsible any individual in the production and marketing chain of livestock who can be shown to have been responsible for having "caused" (by any act of commission or ommission) illegal drug residues in meal, milk, or eggs. Under the revised FDA extra-label drug use policy, a finding of illegal residues is not a prerequisite for initiating regulatory action based on the extra-label use of drugs in food-producing animals.

In case you are not already familiar, "extra-label use" refers to the actual or intended use of a new animal drug in a food-producing animal in a manner that is not in accordance with the drug label directions. This includes, but is not limited to, use in species or for indicating (disease or other conditions) not listed in the labeling, use at dosage levels higher then those stated in the labeling and failure to observe the stated withdrawal time. Extra-label use of drugs is only permitted by the veterinarian and not by laypersons.

The use or intended use of new animal drugs in treating food-producing animals in any manner other than in accordance with the approved labeling causes the drugs to be adulterated under the Act. The Agency will consider regulatory action when such use or intended use is found, whether by a veterinarian, producer, drug distributor or other person. Nevertheless, extra-label drug use in treating food-producing animals may be considered by a veterinarian when the health of the animals is immediately threatened and suffering or death would result from failure to treat the affected animals. In instances of this nature, regulatory action would not ordinarily be considered provided all of the following criteria are met and precautions observed:

1. A careful medical diagnosis is made by an attending veterinarian within the context of a valid veterinarian/client/patient relationship;
2. A determination is made that, (a) there is no marketed drug specifically labeled to treat the condition diagnosed, or (b) drug therapy at the dosage recommended by the labeling has been found clinically ineffective in the animals treated;
3. Procedures are instituted to assure that identity of the treated animals is carefully maintained; and
4. A significantly extended time period is assigned for drug withdrawal prior to marketing meat, milk, and eggs, with steps taken to assure that the assigned timeframes are met, and no illegal residues occur.

Extra-label use of drugs in treating food-producing animals may under this policy, therefore, be considered only in special circumstances. Again I emphasize, the "exempting" criteria do not provide for extra-label drug use by laypersons. Laypersons cannot be expected to have sufficient knowledge and understanding concerning animal diseases, pharmacology, toxicology, drug interactions, and other scientific parameters to use drugs in treating food-producing animals in any way other than as labeled.

Certain drugs may not be used in treating food-producing animals even under the cited criteria. These include chloramphenicol and DES. Extra-label uses of drugs in treating food-producing animals for improving rate of weight gain, feed efficiency, or other production purposes, or for routine disease prevention are inappropriate. Also, the conditions cited above do not provide a basis for the sale and use, for any purpose, of new animal drugs that are not approved.

It is also not acceptable for a veterinarian to enlist the services of a feed mill to mix drugs into a feed on a "prescription" basis. This goes beyond the practice of veterinary medicine, and it is our position that this "third party" relationship makes such uses subject to FDA regulations. The feed mill may only manufacture medicated feeds at levels and uses provided for in the animal drug regulations. There is no extra-label mixing permitted at the feed mill. This is true for mills that sell feed as well as those mills that mix feed for their own animals. We are not likely however to be involved with the on-the farm situation unless the operation is registered with FDA or an illegal tissue residue is found in the marketed animal.

There has been and continues to be the recommendation that all drugs be placed under the direct control of a veterinarian. Perhaps, it would help if I spent a moment to briefly summarize the distinction between prescription (Rx) and over-the-counter (OTC) drug products under Federal regulation. The basis for distinguishing Rx or OTC animal drug products is whether or not it is possible to prepare "adequate directions for use" under which a layperson can use the drugs safely and for the purposes for which they are intended. In effect, the system establishes, when appropriate, a method of distribution and control intended to assure that the Rx product ultimately reaches only the hands of persons trained to use the product. By this I mean the licensed veterinarian or upon the veterinarian's prescription or order, a layperson whom the licensed veterinarian has determined is capable of following directions and of using the product wisely and safely under the veterinarian's supervision. Products for which adequate directions for lay use can be written **must be** labeled for over-the-counter use under existing law. In determining whether directions for use are adequate, an important point for consideration is whether it is reasonably certain the conditions of use prescribed, recommended or suggested in the proposed labeling can be followed in practice.

Safe use includes safety to the animal, safety of food products derived from the animals, safety to the person administering the drug, safety to the persons associated with the animal, and safety in terms of the drug's impact on the environment.

Effective use of a drug product assumes that an accurate diagnosis can be made with a reasonable degree of certainty, that the drug can be properly administered, and that the course of the disease can be followed so that an assessment can be made of the success or lack of success of the product

in terms of its intended use. The assumption also implies that timely adjustment with the dosage or use can be made in the event that recovery is not seen or if an adverse effect from the drug is observed.

The same drug substance may be marketed in a number of different dosage forms and formulations, intended for use by varying routes of administration and in varying species of animals. These may appropriately be labeled "prescription" in some instances and "non-prescription" in other. The primary question is whether adequate directions for use can be written to assure safe and effective use of each individual product. If an average food-animal producer can safely and effectively administer a product, but a companion animal owner, regardless of label directions, cannot administer it safely and effectively, then the prescription status of the product must be different relative to these intended uses. If directions can be written for use for a particular route or administration (IV, IP, etc.) for one animal species but not for another, it is not inconsistent to grant OTC status for the one use and require the Rx legend for the other.

Determining how a veterinary drug product may be marketed is extremely important and the decision is very carefully made after an in depth evaluation of many factors. It is not an arbitrary decision lightly made. For those of you who are interested, we have an internal CVM policy guide, available upon request, which provides guidance to our scientific reviewers on factors to be considered when determing the Rx/OTC marketing status of a drug product before approval.

The important point that I'm trying to make is that the prescription drug status has been designated for a drug product because adequate directions for lay use cannot be written. It has been a long standing agency position that adequate directions for use can be written for drug premixes; thus, their over-the-counter status. We forsee no justifiable reason at this point to unilaterally alter this policy.

We did, however, propose in 1978 to restrict the use of animal feeds containing penicillin, chlortetracycline and oxytetracycline to the order of a licensed veterinarian. This was proposed in concert with two other proposals (both in 1977) intended to restrict the use of these antibiotics because of safety concerns due to transferable drug resistance. The prescription medicated feed proposal called for certain recordkeeping requirements and it was limited to those conditions for use which were provided for in the approved NADAs. No extra-label use was contemplated by this proposal.

The agency postponed decision of this proposal later that same year. We did however, summarize the pertinent comments to the proposal which indicated clearly that neither producer nor veterinarian favored this approach.

Paper presented at the 11th Annual Food Animal Medicine Conference, Columbus, OH, Dec. 5-6, 1985. Dr. Glenn F. Hoffsis, Coordinator.