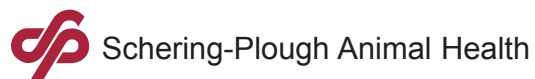




Veterinary Feed Directive (VFD) Drugs:

Impact on Feed Mills Serving the Aquaculture Industry

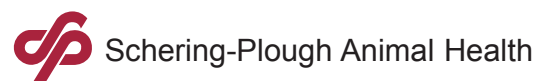


Acknowledgements

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**Veterinary ■
Feed Directive
(VFD) Drugs:
Impact on
Feed Mills
Serving the
Aquaculture Industry**



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Part I: ■ Overview

Introduction

In the past, the Food and Drug Administration (FDA) had only two categories of approved animal drugs: over the counter (OTC) and prescription. Drugs intended for use in animal feeds were classified as OTC drugs, including Category I and II drugs and Type A, B, and C products (see Definitions).

As newer, more effective animal drugs were developed, the FDA's Center for Veterinary Medicine (CVM) recognized that these drugs, particularly antimicrobials, should be approved for use in animal feeds, but that more control over their use was needed than OTC status provided. Prescription drug approvals have been impractical for animal feeds, however, because many states' regulations prohibit feed manufacturers from dispensing prescription drugs.

Concerns about food safety, animal health, and the potential for development of bacterial resistance prompted a coalition of industry and government to come up with a better solution. The result of these efforts, the Federal Animal Drug Availability Act (ADAA) of 1996, established the Veterinary Feed Directive (VFD) and a new category of animal drug, the VFD drug. The final rule implementing the VFD was published in the *Federal Register* in December 2000 (see Regulations).

The feed industry was actively involved in this process, working with the CVM to meet their goals of improved animal health and food safety by requiring veterinary supervision of VFD drugs in animal feeds, while ensuring that the impact on feed manufacturers and their distributors would be minimal. "The establishment of the VFD will enhance prevention and treatment of animal health problems. Effective new therapeutic products will be readily available to producers through normal feed distribution channels. However, the distribution and use of these products will come under close supervision of veterinarians and the Food and Drug Administration," says David A. Bossman, President of the American Feed Industry Association (AFIA).

How will the VFD affect feed mills and their distributors? While the prospect of additional regulations and paperwork may seem daunting, the VFD process is actually quite simple. You'll find all the information needed for compliance with VFD regulations, including definitions of terms, forms and samples of required letters and VFD product labeling, and answers to all your questions on VFD feeds and current good manufacturing practices, in the following sections. Feed mills will need to obtain licensure to manufacture and distribute VFD feeds, and application forms and information are included here as well.

To date, only one new animal drug has been approved by the FDA as a VFD drug, tilmicosin for swine respiratory disease. It is anticipated that the first VFD drug for use

in aquaculture in the United States will be approved later this year. As the AFIA's David Bossman puts it, feed manufacturers and their distributors must understand that "VFD feeds are now a way of life." Rosalie Schnick, National Coordinator for Aquaculture New Animal Drug Applications, adds, "The aquaculture industry—producers, veterinarians, feed manufacturers, pharmaceutical companies—must be prepared do their job as new VFD drugs are approved. As an industry, we want to get it right."

Schering-Plough Animal Health Corporation is pleased to provide feed manufacturers with the information you'll need to be prepared for these new developments in the industry, gathered and presented in one place for easy reference. It is our hope that these materials will facilitate a smooth transition, enabling you to continue to provide your customers with the most effective products as they become available.

Definitions and General Considerations*

Category I: These drugs require no withdrawal period at the lowest use level in each species for which they are approved.

Category II: These drugs require a withdrawal period at the lowest use level for at least one species for which they are approved; or regulated on a “no-residue” basis or with a zero tolerance because of a carcinogenic concern regardless of whether a withdrawal period is required; or are a VFD drug.

Type A Medicated Article: It is intended solely for use in the manufacture of another Type A medicated article or a Type B or Type C medicated feed. It consists of a new animal drug(s), with or without carrier (example: calcium carbonate, rice hulls, corn gluten) with or without inactive ingredients.

Other details: The manufacture of a Type A medicated article requires an approved new animal drug application (21 CFR 514.105).

Type B Medicated Feed: It is intended solely for the manufacture of other medicated feeds (Type B or Type C).

Other details: It contains a substantial quantity of nutrients including vitamins and/or minerals and /or other nutritional ingredients in an amount not less than 25% of the weight. It is manufactured by diluting a Type A medicated article or another Type B medicated feed. The maximum concentration of animal drug(s) in a Type B medicated feed is 200 times the highest continuous use level for Category I drugs and 100 times the highest continuous use level for Category II drugs. The term “highest continuous use level” means the highest dosage at which the drug is approved for continuous use (14 days or more), or, if the drug is not approved for continuous use, it means the highest level used for disease prevention or control. If the drug is approved for multiple species at different use levels, the highest approved level of use would govern under this definition. The manufacture of a Type B medicated feed from a Category II, Type A medicated article requires a medicated feed application (21 CFR 558.4).

Type C Medicated Feed: It is intended as the complete feed for the animal or may be fed “top dressed” (added on top of usual ration) or offered “free choice” (e.g., supplement) in conjunction with other animal feed.

Other details: It contains a substantial quantity of nutrients including vitamins, minerals, and/or other nutritional ingredients. It is manufactured by diluting a Type A medicated article or a Type B medicated feed. A Type C medicated feed may be further diluted to produce another Type C medicated feed. The manufacture of a Type C medicated feed from a Category II, Type A medicated article requires an approved medicated feed mill license application (21 CFR 558.4).

***Source:** For definitions and general considerations and other details of the regulations, refer to Title 21 of the Code of Federal Regulations (CFR), Parts 558.3 and 515.10.

Veterinary Feed Directive (VFD): The VFD is a written statement issued by a licensed veterinarian in the course of the veterinarian’s professional practice that orders the use of a VFD drug in or on an animal feed. This written statement authorizes the client (the owner of the animal or animals or other caretaker) to obtain and use the VFD drug in or on an animal feed to treat the client’s animal(s) only in accordance with the directions for use approved by the FDA. A veterinarian may issue a VFD only if a valid veterinarian–client–patient relationship exists.

Veterinary Feed Directive (VFD) drug: A VFD drug is a new animal drug approved under section 512(b) of the Federal Food, Drug and Cosmetic Act for use in or on animal feed. Use of a VFD drug must be under the professional supervision of a licensed veterinarian.

Medicated Feed Mill License Application (MFMLA): This application (Form FDA 3448) must be submitted only once to FDA to obtain license to manufacture medicated feeds. Form 3448 replaces the Medicated Feed Application (MFA) (Form 1900), which is no longer in use. A commitment to renew registration every year with FDA is required using Form FDA 2556, as defined below. For details see 21 CFR 515.10 and 21 CFR 558.4.

Registration of Drug Establishment/Labeler Code Assignment: An application (Form FDA 2656) to register the feed mill as a drug establishment. It is renewed each year with the FDA as required by 21 CFR 207.20 and 21 CFR 207.21.

Distributor: Any person who distributes a medicated feed containing a VFD drug to another distributor or to the client-recipient of the VFD.

Acknowledgement Letter: A written communication must be provided to a distributor by a consignee who is not the ultimate user of the medicated feed containing a VFD drug. An acknowledgement letter affirms that the consignee will not ship such medicated animal feed to an animal production facility that does not have a valid VFD, and will not ship such feed to another distributor without receiving a similar written acknowledgment letter.

Animal Production Facility: An “animal production facility” is a location where animals are raised for any purpose, but does not include the specific location where medicated feed is made.

Notification Letter: A letter is provided by the distributor to notify the FDA, only once (for each VFD drug), of its intention to distribute animal feed containing a VFD drug. It must include the complete name and address of each business site from which distribution will occur. A responsible person from the firm must sign and date the notification letter. The notification letter must be sent to FDA prior to beginning the first distribution.

Frequently Asked Questions

About Veterinary Feed Directive (VFD) Drugs*

Q: What is the Veterinary Feed Directive?

A: The Animal Drug Availability Act (ADAA) of 1996 established the Veterinary Feed Directive (VFD) and created a new category of animal drug. The final regulations implementing the VFD were published in the *Federal Register* on December 8, 2000 (see the complete text of the regulation in Part IV).

- Prior to passage of the VFD, animal drugs were classified as over-the-counter (OTC) or prescription.
- Prescription status was impractical for drugs used in medicated feeds because many states' regulations prohibit feed manufacturers from dispensing prescription drugs. The VFD is a more practical alternative to prescription status.
- Veterinary diagnosis and supervision is required for use of VFD medicated feeds.
- The VFD will not change the status of OTC drugs approved prior to 2000.
- A *Veterinary Feed Directive order* refers to a written authorization for use. A *Veterinary Feed Directive drug* refers to a new and specific category of drugs.

Q: Why do we need a VFD?

A: The CVM realized that greater control was needed over the use of certain new antimicrobial medications intended for therapeutic use in animal feeds. There were concerns about the development of resistance to antimicrobials, and one of the goals of the VFD is to reduce the rate of development of resistance and prolong the period of effectiveness of these drugs. The feed industry was actively involved in the creation of the VFD to ensure that these goals of improved animal health and food safety were met with minimal disruption of the current medicated feed distribution process.

Q: What does this mean for the feed industry?

A: Manufacturing of VFD feed is no different than manufacturing other medicated feeds containing Category II animal drugs. All VFD drugs will be Category II drugs (see *Definitions*), so feed mills will need to have a valid Feed Mill License to manufacture VFD feeds using the Type A medicated article (see *Definitions*). The major difference is that a VFD form signed by the producer's veterinarian is required to distribute VFD feeds to a producer, and a copy of the VFD form must be kept on file and made available for FDA inspection. Feed mills and distributors will need to learn about the VFD process and comply with all regulations.

*Adapted from the Center for Veterinary Medicine Guidance for Industry 120: Veterinary Feed Directive Regulation and fact sheets from the Veterinary Feed Directive Coalition.

Q: What are the steps in the VFD process?

- A:**
- The producer contacts a veterinarian for diagnosis and treatment.
 - The veterinarian makes a determination that a VFD medicated feed is necessary within the Veterinarian-Client-Patient Relationship (VCPR).
 - The veterinarian issues a signed VFD order by including all of the information needed for a valid VFD or by filling out the drug supplier's preprinted form (if available) and giving it to the producer.
 - The producer uses the VFD to order the feed from a feed supplier. A VFD feed may not be distributed to a producer without a signed VFD form.
 - Licensed feed manufacturers and distributors that ship a VFD feed to a downstream distributor or retailer must receive and retain a copy of a written acknowledgement stating that the VFD feed will be further distributed only in accordance with FDA requirements.
 - The veterinarian who issues the VFD, the producer, and the person or company supplying the VFD feed must retain copies of the signed VFD form for a minimum of two years.

Q: Has the FDA approved any drugs as VFD drugs yet?

A: The first, and to date the only, drug approved by the FDA as a VFD drug is Pulmotil® 90 Type A Medicated Article (tilmicosin). It is an antimicrobial for use in the control of swine respiratory disease associated with *Actinobacillus pleuropneumoniae* and *Pasteurella multocida*.

Q: What information is required on the VFD form?

A: Preprinted VFD forms will most likely be supplied by each VFD drug's sponsor (the pharmaceutical company), although the CVM does allow veterinarians the option to make up their own forms. (A sample VFD form is provided in Part II following Richard Seller's article on VFD drugs.)

The form must include the following:

- Client's name, address, telephone, and if the VFD is faxed, facsimile number
- Identification and number of animals to be treated/fed the medicated feed, including the species and location of the animals
- Date of treatment, and if different, date of prescribing the VFD drug
- Approved indications for use
- Name of the animal drug
- Level of animal drug in the feed, and the amount of feed required to treat the animals

- Feeding instructions with the withdrawal time
- Any special instructions and cautionary statements necessary
- Expiration date of the VFD order
- Number of refills (reorders) if necessary and permitted by the approval
- Veterinarian's license number and name of state issuing the license
- The statement "Extra-label use (i.e., use of this drug in a manner other than as provided for in the VFD drug approval) is strictly prohibited."
- Any other information required by the specific VFD drug approval regulation

Q: What are the responsibilities of the veterinarian, the producer, and the feed mill/distributor in the VFD process?

A:

The Veterinarian's Responsibility:

- Be appropriately licensed.
- Write orders for VFDs only under the context of a valid veterinarian-client-patient relationship.
- Prepare and sign a written VFD order in triplicate providing all requested information.
- Provide the feed distributor with the original VFD order directly or through the client.
- Give a copy of the VFD order to the producer.
- Retain a copy for your records for a minimum of two years.
- Provide VFD orders for review and copying by FDA during inspections.
- Write VFD orders only for drugs approved as VFD drugs.
- Determine how long the VFD will be valid for, within FDA-approved limitations. The expiration date should be included as specified in the regulations.
- If the VFD form cannot be hand delivered, it can be faxed or e-mailed. Within five working days, the veterinarian must assure that the original VFD order is received by the distributor. A veterinarian cannot issue a VFD order over the phone.
- If necessary, the veterinarian can issue another VFD, using a new form, when the previous VFD expires.

The Producer's Responsibility:

- Contact the veterinarian to diagnose and treat animal(s).
- Agree to follow the veterinarian's recommendations
- Provide the original VFD order to the feed supplier if the veterinarian has not done so.

- No producer may obtain a VFD medicated feed or a VFD premix from any source, including a commercial feed company, without a valid VFD unless the producer is also a distributor of VFD medicated feeds or has a FDA feed mill license.
- Producers may purchase VFD products in Type B (premix) or Type C (ready to feed) form. Producers may purchase Category II Type A premixes if they hold a valid feed mill license.
- Producers can manufacture VFD medicated feeds if they hold a valid medicated feed mill license and comply with current good manufacturing practices (GMPs).
- Keep a copy of the VFD order for a minimum of two years.
- Provide VFD orders for review and copying by FDA during inspection.
- Administer the VFD feed to the animal(s).

The Feed Mill/Distributor's Responsibility:

- Maintain a valid Medicated Feed Mill License (FML) Application (Form 3448), and renew registration each year with the FDA using Form 2656 as required by 21 CFR 207.20 and 21 CFR 207.21.
- Retain original VFD order supplied by the veterinarian or producer for two years.
- Provide VFD orders for review and copying by FDA during inspections.
- Possess current approved Type B and/or Type C Medicated Feed labeling for each Type B and/or Type C Medicated Feed to be manufactured prior to receiving the Type A Medicated Article containing the drug.
- Notify the FDA only once, by letter, of your intent to manufacture and/or distribute feed containing the VFD drug.
- Obtain an acknowledgment letter from all consignees who distribute but are not the ultimate user of the feed.
- Notify the FDA within 30 days of any change in name or business address.
- Ensure that all labeling and advertising prominently and conspicuously displays the following cautionary statement:

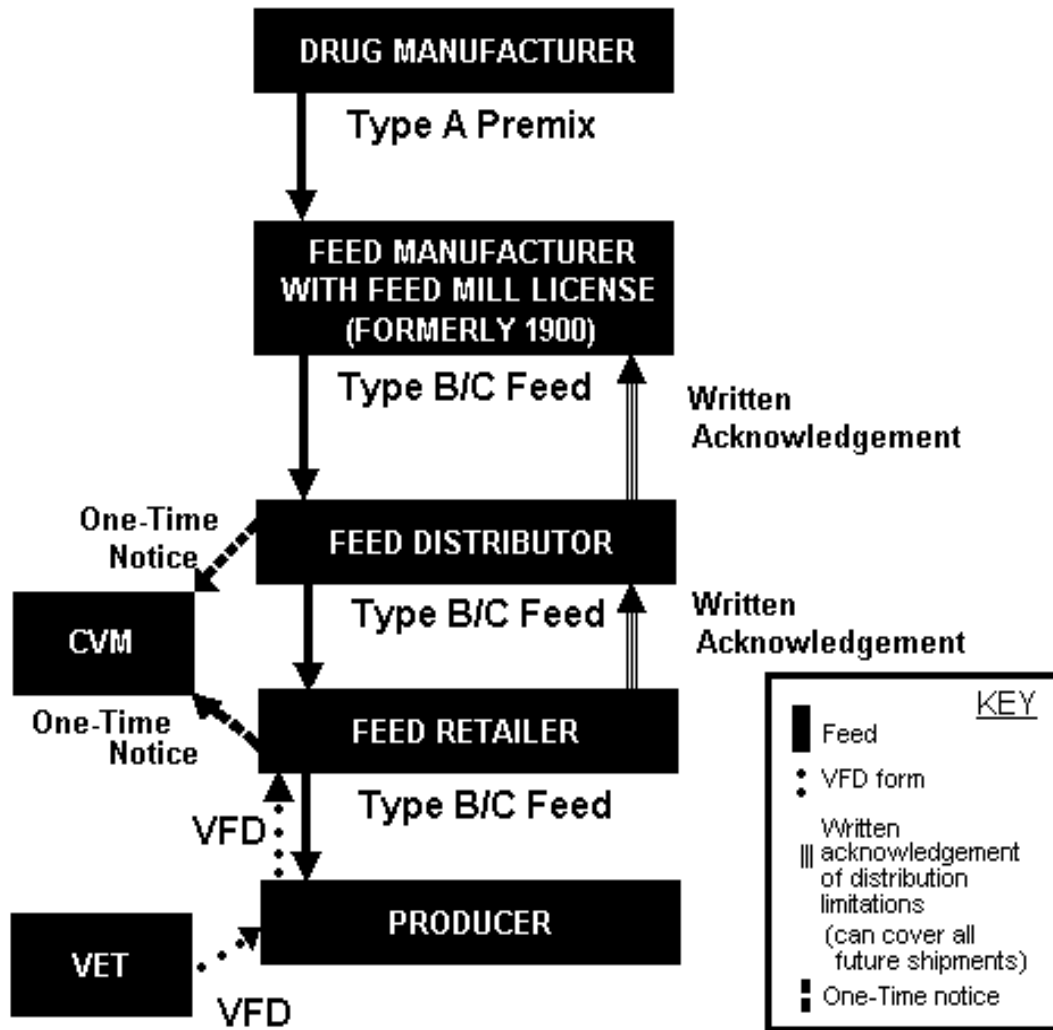
“Caution: Federal law limits this drug to use under the professional supervision of a licensed veterinarian. Animal feed bearing or containing this veterinary feed directive drug shall be fed to animals only by or upon a lawful veterinary feed directive issued by a licensed veterinarian in the course of the veterinarian’s professional practice.”

Q: Are there any special paperwork requirements for VFD feeds?**A:** Yes; there are three types of paperwork involved in the distribution of VFD feeds:

- First, the person or firm (whether or not a licensed feed mill) supplying a VFD feed to a producer must receive and retain a **copy of the signed VFD form** issued by the producer's veterinarian. *(See the sample VFD form following Richard Sellers' article on VFD feeds in Part II.)*
- Second, licensed feed manufacturers and distributors that ship a VFD feed to a downstream distributor or retailer for inventory must receive and retain a written **acknowledgement letter** stating that the VFD feed will be further distributed only in accordance with FDA requirements. *(See the sample acknowledgement letter following Richard Sellers' article on VFD feeds in Part II.)*
- Third, distributors must send a **notification letter** to the FDA of their intent to distribute products containing VFD drugs. This letter must be sent within 30 days after beginning distribution. *(See the sample notification letter following Richard Sellers' article on VFD feeds in Part II.)*

Three different distribution scenarios, with the corresponding paperwork requirements indicated, are illustrated in the schematic diagrams on the following pages.

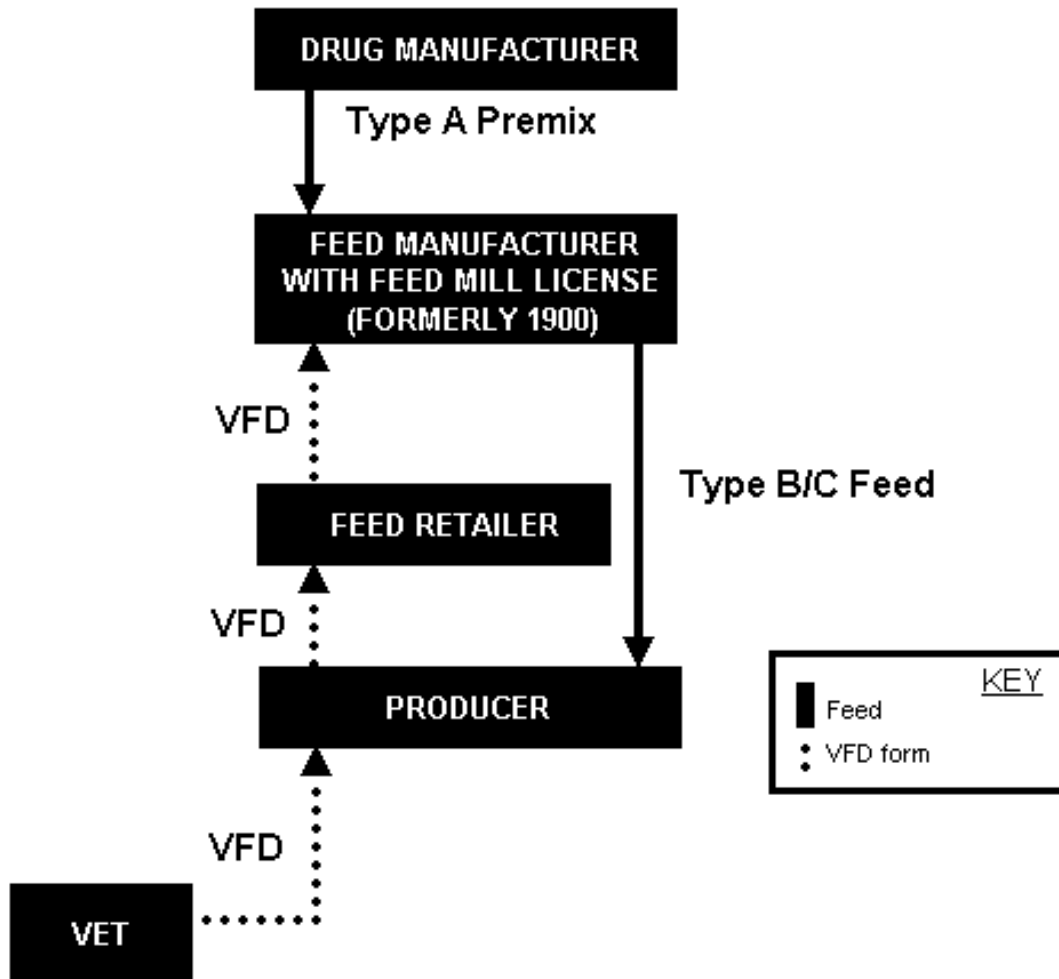
Basic VFD Feed Distribution Schematic



The paperwork requirements for manufacture, distribution, and use of VFD medicated feeds are shown for the basic VFD feed distribution system.

(Diagram courtesy of the Veterinary Feed Directive Coalition.)

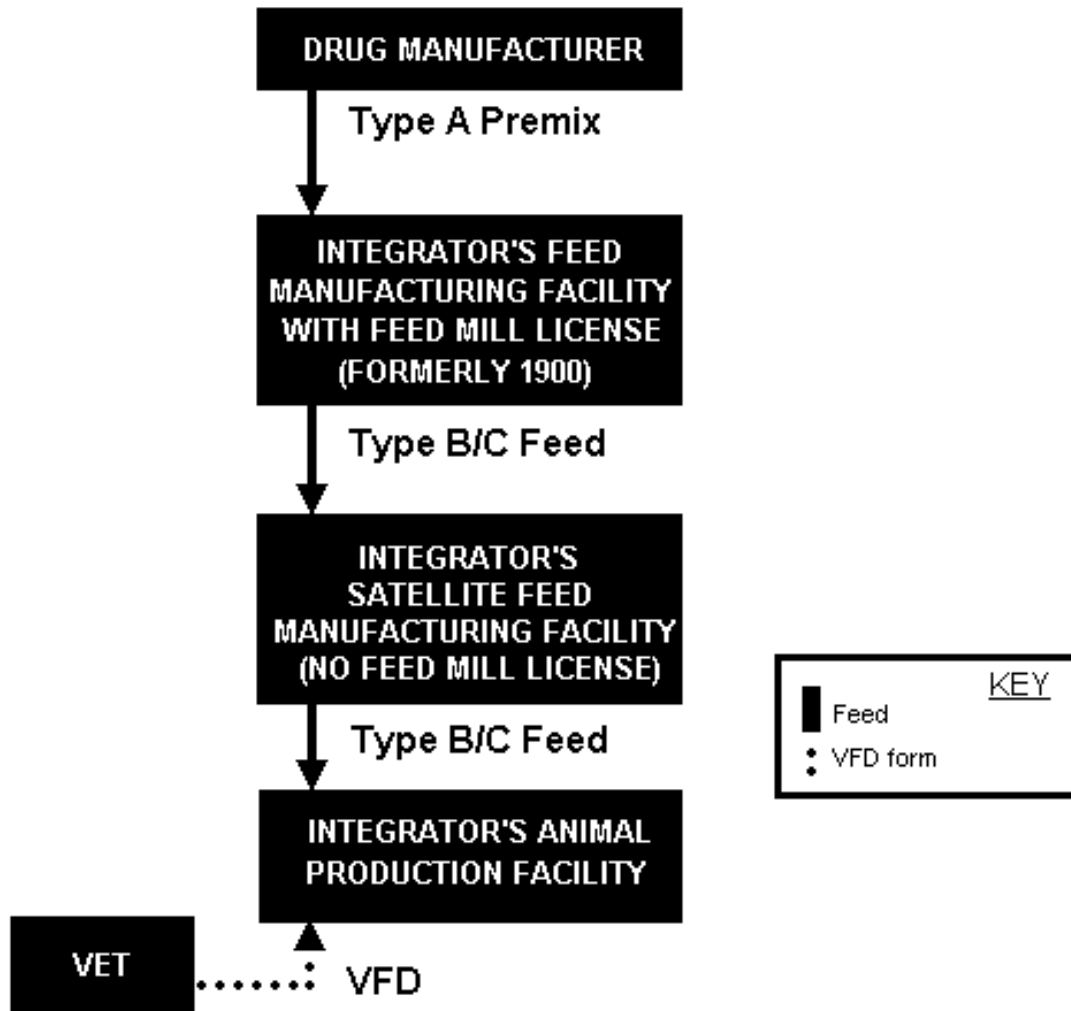
“Direct Ship” VFD Feed Distribution Schematic



The paperwork requirements for manufacture, distribution, and use of VFD medicated feeds are shown for the “direct ship” VFD feed distribution system.

(Diagram courtesy of the Veterinary Feed Directive Coalition.)

Integrator VFD Feed Distribution Schematic



The paperwork requirements for manufacture, distribution, and use of VFD medicated feeds are shown for the integrator VFD feed distribution system.

(Diagram courtesy of the Veterinary Feed Directive Coalition.)

Q: What is the responsibility of the feed distributor if the VFD form is not completely filled out?

A: The feed distributor should not fill an order that does not have all the required information. The responsible veterinarian should be notified that the order may not be filled until all the necessary information on the VFD order is provided.

Q: Is there an alternate method by which a VFD order can be transmitted to the feed distributor?

A: According to the CVM, if a situation occurs in which prompt hand delivery of a VFD order may not be possible, but immediate delivery of a VFD feed is necessary, transmission of the form by facsimile (fax) or other electronic means (e-mail) is permitted provided safeguards are in place to prevent misuse (21 CFR, Part 11). *(E-mail transmission probably will be impractical, however, because the ruling in effect requires validation of computer hardware and software, which most veterinarians are unlikely to do.)* The distributor must receive an original signed VFD order within 5 working days of receipt of the facsimile or electronic document. **Telephone orders are not allowed.**

Q: Who is held responsible, the veterinarian, the client (feeder), or feed distributor if the actual VFD order is not properly distributed?

A: While all bear responsibility, the veterinarian is most in control. Thus, CVM believes it is the veterinarian's obligation to assure that the original VFD order is distributed to the feed distributor with the timeliness required.

Q: Is a feed mill or feeder permitted to distribute or feed an unapproved drug product that is requested by a veterinarian in a VFD order?

A: A feed mill may not fill an order and the client may not feed a VFD feed to his/her animals that is in violation of FDA drug approval.

Q: What mechanisms are in place to discourage the producer from faxing the order to multiple feed mills, thus abusing the drug?

A: While the possibility exists that a client may submit a copy of the VFD order to several distributors to obtain additional VFD feed, the distributor will become aware of the irregularity when the original VFD order does not arrive within 5 days as required by the regulation.

Q: Does the manufacture of a medicated feed containing a VFD drug require a feed mill license?

A: Yes. Classifying a drug in Category II adds additional regulatory controls because feed manufacturing facilities must possess a medicated feed mill license and be registered with the FDA in order to manufacture a Type B or Type C medicated feed from a Category II, Type A medicated article. Registered feed mills are required to be inspected at least every 2 years. Such inspections will help the agency ensure that VFD requirements are met. *(Form 3448, the Medicated Feed Mill License Application, is included in Part III.)*

Q: What is the distributor notification process?

A: All distributors must notify the CVM of their intent to distribute medicated feed containing a VFD drug. This is a one-time only occurrence. Distributor, in this case, means any person who distributes a medicated feed containing a VFD drug to another distributor or to the client-recipient of the VFD. A distributor notification must include the name, address (both physical and mailing, if different) and be sent to: Center for Veterinary Medicine, HFV-226, 7500 Standish Place, Rockville, MD 20855. *(See the sample notification letter following Richard Sellers' article on VFD feeds in Part II.)*

Q: Under what circumstances must an updated notice be submitted to the FDA?

A: An updated notice is required within 30 days of any change in name or business address.

Q: How is the notification letter different from the acknowledgement letter?

A: A notification letter is a one-time notice by an individual or company of its intent to distribute a medicated feed containing a VFD drug. An acknowledgement letter is sent to the distributor by a purchaser who is not the ultimate user of the feed stating that the VFD feed will be sold only to a producer with a valid VFD order, or to another distributor who provides a similar acknowledgement letter. *(See the sample acknowledgement letter following Richard Sellers' article on VFD feeds in Part II.)*

Q: How does this regulation deal with refills, reorders, or the length of time a VFD order is valid?

A: CVM believes there are situations when refills and expiration dates, possibly of several months, are appropriate to medicate multiple production groups and provide efficient treatment of sick animals, and that allowances of this type will vary considerably. Because CVM can not predict what types of drugs and disease situations will be

presented in the future, the issue of refills and reorders and the duration of time a VFD order is valid will be considered on a drug-by-drug basis as part of the new animal drug approval process.

Q: If a VFD order is written for refills and the subsequent orders are filled at a different establishment than the first, how do both establishments retain the original order?

A: It is possible the VFD order may be required by one distributor first and later by another for refill. The regulation requires that a feed establishment retain the original copy of the order for 2 years, thereby making it impossible to forward the original VFD order to another establishment. In these situations, the client should contact the issuing veterinarian and request a new VFD order.

Q: Is there any special labeling for VFD feeds?

A: Type A medicated article labels will be approved by the FDA and will be supplied by the VFD drug sponsor (the pharmaceutical company). Labels for Types B and C feeds will also be approved for each VFD product. Manufacturers of type B and C feeds should label the feeds in accordance with the approved labels, which can be obtained from the drug manufacturer. The labels will contain the following cautionary statement about VFD and feeding:

“Caution: Federal law limits this drug to use under the professional supervision of a licensed veterinarian. Animal feed bearing or containing this veterinary feed directive drug shall be fed to animals only by or upon a lawful veterinary feed directive issued by a licensed veterinarian in the course of the veterinarian’s professional practice.”

A sample label for a Type A Medicated Article containing a hypothetical VFD drug, Healwell, is shown on the following page.

Healwell (anycycline) Type A Medicated Article

CAUTION: Federal law limits this drug to use under the professional supervision of a licensed veterinarian. Animal feed bearing or containing this veterinary feed directive drug shall be fed to animals only by or upon a lawful veterinary feed directive issued by a licensed veterinarian in the course of the veterinarian's professional practice.

Indications: Healwell is indicated for the control of animal respiratory disease associated with *A. bacillus*.

CAUTION: The safety of anycycline has not been established in pregnant animals or animals intended for breeding purposes.

Warning: Avoid inhalation, oral exposure, and direct contact with skin or eyes. Thoroughly mix and handling Healwell should use protective clothing, impervious gloves, goggles, and NIOSH-approved dust mask. Wash thoroughly with soap and water after handling. If accidental eye contact occurs, immediately rinse thoroughly with water. If irritation persists, seek medical attention. Not for human consumption. Keep out of reach of children. The Material Safety Data Sheet contains more detailed occupational safety information. To report adverse events to users, to get more information, or to obtain a material safety data sheet, call 1-800-555-1234.

Mixing: Thoroughly mix Healwell Type A Medicated article or Type B medicated feed to provide a complete Type C medicated feed containing 200-400 per ton. Do not use in concentrates or feeds containing bentonite. Bentonite in feeds may affect the efficacy of anycycline.

Starting concentration of Healwell Type A Medicated Article grams per pound	Amount of Type A Medicated Article to add per ton pounds	Resulting concentration in Type C Medicated Feed grams per ton
100	4	400
	3	300
	2	200

Starting concentration of Healwell Type A Medicated Article grams per pound	Amount of Type B Medicated Feed to add per ton pounds	Resulting concentration in Type C Medicated Feed grams per ton
20	20	400
	15	300
	10	200

For Technical Service Call: 1-800-555-1234
 Avoid moisture and excessive heat (40°C)
 Not to be used after the date printed on the bag.
 NADA xxx - xxx, Approved by FDA

Know Animal Health
 Anytown, MD 12345, USA



A sample label for a Type A Medicated Article containing a hypothetical VFD drug, Healwell.

Q: Will the introduction of VFD feeds result in changes in FDA or state inspection of my business?

A: For feed manufacturers and distributors, FDA and state inspectors likely will ask to see written acknowledgments from downstream distributors and retailers to whom you supplied VFD feeds. Dealers or manufacturers who delivered VFD feeds to producers may also be asked to allow the inspector to examine files of the VFD forms that were issued by the producer's veterinarian.

Q: Are there any changes in current Good Manufacturing Practices (CGMPs) specific to the manufacture of VFD medicated feeds?

A: No additional CGMPs are required for the manufacture of VFD medicated feeds. (See Richard Sellers' article on GMPs for Medicated Feeds in Part II; the article is followed by the text of the FDA's CGMP Regulations for Feeds.) However, as mentioned earlier, there are labeling requirements specific to VFD medicated feeds.

Q: Are the testing requirements for VFD medicated feeds any different from those required for feeds containing other Category II drugs?

A: The required laboratory controls or assays for VFD medicated feeds are no different than those for feeds containing other Category II drugs.

Q: May I advertise VFD feeds?

A: Yes, however, all promotional labeling and advertising for a VFD drug or feed must include the FDA-required cautionary statement.

Q: Are feed manufacturers allowed to dilute and inventory VFD feeds?

A: Yes. Feed manufacturers holding a feed mill license may inventory and dilute VFD products. A distributor or retailer that does not hold a feed mill license may inventory and dilute Type B and Type C feeds. Except for some special paperwork requirements to manufacture and sell, a VFD feed is no different than manufacturing or selling any medicated feed containing a Category II animal drug.

Q: Are there special requirements for returning feed containing VFD drugs?

A: No.

Part II: ■

From the

Literature

Use of Veterinary Feed Directive Drugs in Feeds



By Richard Sellers

Richard Sellers is vice president of feed control and nutrition for the American Feed Industry Assn., a national trade association representing the interests of more than 700 feed manufacturers, distributors, ingredient suppliers, equipment manufacturers, nutrition consultants and animal health distributors. He holds a B.S. from the University of Memphis and an M.S. in poultry science from the University of Arkansas.

The Animal Drug Availability Act of 1996 (ADAA) authorizes a new category of animal drugs, veterinary feed directive (VFD) drugs. Before this law was enacted, only two categories of animal drugs existed, over-the-counter (OTC) or prescription (Rx). Animal drugs approved for use in feeds were all available OTC. However, VFD drugs are something in between OTC and Rx animal drugs.

The VFD process was developed by a coalition of animal health companies, the feed industry, veterinarians, producers and regulatory officials to better control new therapeutic, antimicrobial animal drugs. VFD was offered as a better, more practical alternative to Rx drugs for feed, and one less likely to cause disruptions of the medicated feed distribution process.

FDA published a final rule Dec. 8, 2000, to implement VFD. It was effective Jan. 8, 2001.

All animal drugs must still be approved by FDA's Center for Veterinary Medicine (CVM). The determination of whether a drug will be approved as a VFD drug or as an OTC drug is made by CVM. Similarly, VFD drugs will all be Category II animal drugs requiring a feed mill license (FML) for using the Type A medicated article. Also, combinations of drugs containing VFD drugs are limited to those combinations approved by FDA.

Use of VFD drugs in an extra-label fashion is prohibited by law. Neither veterinarians nor producers may change the drug level approved in the animal drug regulation, the species or indications for use for any drug used in animal feed, including VFD drugs.

FDA officials have stated that only certain animal drugs approved after ADAA was signed into law will be made VFD drugs. It appears unlikely that currently approved drugs will become VFD drugs.

The first VFD drug was approved in 1996. Widespread marketing of this drug began six months later. Within this animal drug's approval regulation, FDA specified the information required on a VFD form. A sample form follows this article detailing the required information, and I recommend veterinarians use such a form. Moreover, there are two letter forms also

The Veterinary Feed Directive (VFD) process is a simple one designed by a coalition of animal agriculture to ensure new therapeutic animal drugs are used safely and in accordance with current science. Feed manufacturers, dealers, retailers, producers and veterinarians must insure there is adequate control of VFD products. This chapter looks at the VFD process and associated dealer requirements and liability issues.

following this article, but FDA has not approved any of these VFD forms for use, although the ADAA requires filing information with FDA and maintaining copies of VFDs and required statements and having them available for inspection review.

THE VFD PROCESS

Use of a VFD is relatively

simple. The first step in the VFD process is for a producer to receive a signed, lawful VFD on a preprinted, multi-part form. Normally, VFD forms will be specific for one drug. The form has at least three copies: one each for the veterinarian, the producer and feed supplier.

FDA's final rule on VFD does allow for facsimile transmission of VFD forms by a veterinarian, provided that the veterinarian sends the signed original within five working days. The client (producer), distributor and veterinarian must keep these copies for two years.

The regulation prohibits telephone VFDs, but allows electronic transmission (e-mail) provided that the sender has complied with 21 CFR, Part 11, Electronic Records & Electronic Signatures. Since this rule essentially requires validation of computer hardware and software, it is unlikely veterinarians can comply with this provision. Therefore, electronic transmission of VFD forms will be unlikely.

The producer takes the signed VFD to his feed distributor, which may be a feed manufacturer or dealer. He gives the feed supplier one copy of the signed VFD form, and the supplier fills his request with existing feed or manufactures a specific feed with the VFD drug level required on the VFD form. The feed supplier must maintain the VFD forms for two years at the facility fulfilling the VFD request.

The VFD form may request either a Type B or Type C medicated feed to be delivered to the producer. If the VFD indicates a Type B, then further mixing is required prior to feeding.

Two additional forms may be required for those handling medicated feeds containing any VFD drugs. One notifies FDA of a facility's intent to distribute products containing VFD

drugs. This should be completed and sent to FDA within 30 days after beginning distribution. From these notifications, FDA will likely develop a list of VFD feed suppliers. A sample copy of the FDA notification letter follows this article.

The second form is provided to the feed manufacturer from a dealer or from a dealer to another dealer. This form (or letter) says that medicated feed containing VFD drugs (i.e., VFD feeds) will not be further distributed by the dealer providing the form without receiving a signed VFD form or letter from another supplier or dealer that they will not distribute VFD feeds without a signed VFD form or similar acknowledgement. In other words, you may not receive VFD products from a feed manufacturer unless you promise only to distribute VFD feeds to producers who present a signed VFD form, or you promise only distribute to dealers who will sign the same form. If you receive an acknowledgement letter from your dealer-customer, you must maintain a copy of the letter for two years after the last feed shipment covered by the letter.

Both of these forms need only be supplied to the recipients one time.

The first VFD drug is a Category II drug requiring an approved feed mill license (FML) in order to receive the Type A medicated article. Otherwise, no FML is required to receive any other VFD feed.

CGMP ISSUES RELATED TO VFD

Although VFD requires some additional paperwork, no additional current good manufacturing practice (CGMP) regulations are required. However, additional labeling requirements are mandated by the act, which states that VFD products must contain a caution statement, such as, **“Caution: Federal law limits this drug to use under the professional supervision of a licensed veterinarian. Animal feed bearing or containing this veterinary feed directive drug shall be fed to animals only by or upon a lawful veterinary feed directive issued by a licensed veterinarian in the course of the veterinarian’s professional practice.”**

For inspection purposes, feed manufacturers that sell exclusively through dealers will not see any VFD forms in their daily business.

The feed dealer need not supply copies of the VFD form to the feed manufacturer.

The VFD preprinted form will likely contain mixing or feeding directions or information. This form may constitute part of the required medicated feed labeling accompanying a product.

In the negotiations to enact the ADAA, some groups believed licensed feed mills did not need to notify FDA of the firm’s intent to distribute VFD products, as these mills already registered with FDA because they hold approved feed mill licenses. Since the statute does not grant such exceptions, it is suggested that each firm handling VFD products simply notify FDA using the form that follows this article.

A signed VFD form constitutes a required CGMP production and/or distribution record and as such would have to be maintained at FDA licensed facilities. Although CGMP regulations require general record retention of one year, FDA’s VFD rule requires VFD-related records be retained for two years.

Although a feed manufacturer may manufacture VFD feeds without a signed VFD, the VFD feed should not be unloaded at a producer’s production facility without a signed VFD form in the feed supplier representative’s possession. This may present a difficult situation at times, but it is unlawful to provide a VFD feed to a producer without a valid, signed VFD form. One issue that was not clearly resolved by the VFD final rule was that of reorders. Although the rule says refills are governed by the individual drug regulation, some firms are seeing VFD forms for

multiple facilities, such as all starter pigs raised in a facility for a 6-12 month period, even though a single VFD for the drug tilmicosin is for 28 days.

At issue is the difference between “refill” and “reorder.” A refill is normally reissuing the VFD for the same animals and the same drug and level, which is not allowed for tilmicosin. However, a reorder is being used by veterinarians for different animals going into the same house for the same drug and level. Although this does not constitute a refill, it is not clear in the final rule.

VFD FORM

FDA is not expected to issue VFD forms due to the requirement for all government forms to be approved by the Office of Management & Budget.

It is likely the pharmaceutical industry may choose to standardize the VFD form and issue pre-printed, multi-part drug specific forms. Some organizations have called for numbered forms to further aid in traceback of VFD drugs.

The required information on the VFD form is listed on a sample form following this article. Briefly, the form must contain the following:

- Veterinarian’s name, address and phone number
- Producer’s name, address and phone number
- Species, number and location of animals to be treated
- Date of treatment
- Condition or disease being treated
- Name of VFD drug
- Mixing or feeding directions with any withdrawal time
- Amount of drug to be mixed and amount of feed
- Any warning statements (including VFD warning statement) or special instructions
- Expiration date of the VFD
- Number of refills (if permitted)
- Veterinarian’s signature, license number and licensing state
- Location of VFD drug supplier (optional)

DEALER REQUIREMENTS

Feed dealers or suppliers of VFD feeds have certain requirements to which they must adhere that are not part of handling other medicated feeds. First, the dealer must receive a valid, signed VFD form before selling a VFD feed to a producer. Moreover, after receipt of the first VFD shipment, the dealer or supplier must notify FDA of the dealer’s intent to distribute VFD products.

This is accomplished by utilizing the form letter following this article.

Upon receipt of any signed VFD forms and delivery of VFD feeds, the dealer or feed supplier must maintain VFD forms for a period of at least two years after distribution of the last VFD feed.

Dealers may not ship to other dealers unless the recipient has signed an acknowledgement letter, such as that following this article, indicating the second dealer will not sell VFD feeds without a valid VFD form or similar acknowledgement from other dealers to which any VFD products are to be delivered. Dealers receiving these acknowledgement letters from their dealer-customers must maintain a copy for two years after the last feed shipment covered by the letter.

Remember, a signed VFD must be in the hands of the dealer before delivery of VFD feeds to the producer can occur.

If a dealer is only able to deliver a partial load, the dealer should acknowledge such partial shipment on the VFD form. For subsequent shipments in fulfillment of the VFD order, the dealer may mix the entire load and hold it in the dealer’s bins or bags, or mix a partial load and mix the remaining portion at a later date.

For feed manufacturers to direct ship VFD feeds from an order received via a feed dealer, the dealer or retailer must supply a copy of the VFD to the feed manufacturer. This may be done by supplying an original copy, photocopy or telefacsimile. Feed manufacturers do not need to maintain VFD forms from dealers who ship to producers directly.

LIABILITY ISSUES

Product liability issues do not change with use of VFD products. If feed manufacturers have a reason to doubt the authenticity of a veterinarian's signature, the feed mill can phone the veterinarian or producer to confirm the VFD or call the state licensing authority for confirmation. Normally, this should not be a problem. If the feed manufacturer doubts the VFD form's indications for use or other information, the mill can contact either the veterinarian or producer to confirm the information. Feed mill personnel are not in a position to second-guess a veterinarian's diagnosis but have some obligation to insure the information on the VFD form is reasonably accurate, complete and complies with the federal regulations.

Regarding regulatory liability issues, state feed control officials may place under stop sale order VFD products at dealers who sell VFD products without the required documentation,

i.e., signed VFD forms or written acknowledgements. Other stronger regulatory actions are available also, such as condemnation of feed, injunctions or criminal sanctions.

SUMMARY

The VFD process is a simple one designed by a coalition of animal agriculture to ensure new therapeutic animal drugs are used safely and in accordance with current science. Feed manufacturers, dealers, retailers, producers and veterinarians must insure there is adequate control of VFD products. Correct forms must be utilized, correct information must be provided, mixing instructions must be followed and records must be maintained for the specified time frames. Failure to perform one of these mandatory and important functions may result in not only regulatory sanctions, but could result in FDA further restricting VFD product use or FDA failing to approve more of these important animal health products.

The VFD process is vital to animal producers who need new therapeutic agents.

The process also assures the consuming public that new, therapeutic agents will be safely and correctly used.

Remember, take time, read and follow directions for all animal health products. ■

Notice To FDA of Distribution of VFD Feeds

I/We hereby notify the Food & Drug Administration that I/we have begun distributing VFD feeds.

Signature

Name of responsible party
(please print or type)

Name of Firm or Individual

Business Address

Site address if different from above

City/State/Zip

Date

Send this form to:

Division of Animal Feeds (HFV-226)
Center for Veterinary Medicine
Food & Drug Administration
7500 Standish Place
Rockville, MD 20855
FAX 301/594-1812

Acknowledgement Of Distribution Limitations For VFD Feeds

I/we hereby acknowledge that, as required by federal law, I/we shall distribute VFD feeds received by me/us from [name and address of feed supplier] only as follows:

- (1) To an animal production facility, if the owner or operator of that facility provides me/us with a copy of a veterinary feed directive (VFD) covering the quantity of feed involved and the animal production facility to which the feed is being distributed; or
- (2) To another person for further distribution, if that person provides me/us with a written acknowledgement similar to this acknowledgement.

Signature

Name of Firm or Individual

Business Address

City/State/Zip

Date

Send this form to each of your firm's suppliers of VFD products.

Veterinary Feed Directive

Client _____
Address _____

Phone _____

Veterinarian _____
Address _____

Phone _____

Animals to be treated (number and location):

VFD Drug:

HEALWELL®
(anyglycosylated)

Mixing Direction: (See reverse for additional mixing information)

Mix into type C Medicated Feed to provide: 200 _____ 100 _____
(Check only one)

Warning: Feeds containing _____ be withdrawn 9 days prior to slaughter.

Feeding Instructions: Feed _____ as the sole ration for 21 days
beginning with onset of symptoms.

Special Instructions: _____

Expiration date: _____ Refills (if permitted): _____
Month/Day/Year

Total amount of Type C feed to be received under this VFD: _____ tons

Veterinarian's Signature: _____ Date: _____
License Number: _____ State: _____

This VFD drug will be obtained from: _____

See reverse side for important product information.

HEALWELL® is the registered trademark of Know Animal Health.

Current Good Manufacturing Practice regulations for medicated feeds



By Richard Sellers

Richard Sellers is vice president of feed control and nutrition for the American Feed Industry Assn., a national trade association representing the interests of more than 700 feed manufacturers, distributors, ingredient suppliers, equipment manufacturers, nutrition consultants and animal health distributors. He holds a B.S. from the University of Memphis and an M.S. in poultry science from the University of Arkansas.

Medicated feed manufacturers are subject to current good manufacturing practice regulations (CGMPs) and should be aware of the purpose and origin of the term. In understanding such origin and purpose, manufacturers should be better equipped to comply with the provisions of the regulations.

The regulations in general are very specific but open to interpretation about how to comply. Generally, there are few problems resulting from interpretation differences, but medicated feed manufacturers should be aware that differences of opinions can and do occur over the meaning of the regulations. Several differences are discussed below.

SOURCE OF TERM

The term is found in the Federal Food, Drug & Cosmetic Act, where it is stated that products may be deemed to be adulterated if they are not produced in conformance with “current good manufacturing practices.” Note the word current, which means present or today, not the past or future. Note also that the standard is the conditions under which the product is produced, not the condition of the product itself. Actual adulteration is not necessary. If the conditions of production are less than currently accepted and generally practiced by industry — as described in the CGMP regulations, the product can be deemed adulterated from a regulatory perspective. Hence, compliance with CGMPs is a practical necessity.

CGMP PHILOSOPHY

Requiring compliance with CGMPs is, in effect, an expression of regulatory philosophy. It is a “before the fact” preventive type approach to the control of medicated feeds. Compliance with CGMPs should insure, to the extent possible, that medicated feeds will be proper in all respects as to drug content and labeling and furthermore, that medicated feed production will not compromise other medicated feeds or non-medicated feeds. Compliance with CGMPs by the medicated feed manufacturer is intended to provide the Food & Drug Administration with reasonable assurance that there is proper use of animal drugs. The alternative is an “after the fact” program of sampling

Current good manufacturing practice regulations (CGMPs) for medicated feeds are those practices reflecting available information accepted by the majority of reputable feed manufacturers. CGMPs are neither stagnant nor are they only one person’s opinion. An explanation of the purpose of the regulations is provided here and followed by the full text of the regulations.

and testing to uncover any problems. Prevention is more efficient and effective.

INDUSTRY STANDARD

CGMPs are an industry standard in the format of FDA’s regulations. They are adopted through the rule-making process and have the effect of law.

CGMPs are those practices

reflecting available information accepted by the majority of feed manufacturers. CGMPs are neither stagnant nor are they only one person’s opinion. Therefore, these practices will vary depending on a variety of issues, such as drug used, type of equipment, physical facilities and customer served.

GOOD BUSINESS PRACTICES

While specific practices will vary, there are some common threads of good business practice. There is strong reliance on good housekeeping, inventory controls, a meaningful documented history of production tied to responsible individuals and the ability to trace and locate product in the field if necessary — and likewise to trace product back from the field and back through the process of its production if this is necessary. Operation should be on a predetermined, systematic and documented basis.

INDUSTRY INPUT/CGMP PRINCIPLES

Industry — through the American Feed Industry Assn. — contributed in a significant manner to the original FDA feed CGMP regulations implementing the CGMP provision of the law and had substantial input into the current version. This contribution was appropriate since AFIA’s feed manufacturing members are the professionals in this regard who hold the expertise on good manufacturing practices. The current version of the CGMP regulations mirrors the principles set forth in the first set of regulations. Prominent in those principles is the fact the CGMP regulations provide a high degree of flexibility in achieving specific end points. In effect, objectives are specified and means to achieve them outlined, with flexibility provided on how to meet these objectives. This is a departure from the norm. Usually regulations are rather specific rules implementing provisions of law. The difference with the CGMP regula-

tions is directly related to the wide variety of feed manufacturing-mixing facilities and products and the need for flexibility in determining and applying CGMPs. Flexibility is also needed to keep current, since current means a moving target as time passes. The increasing use of computerized controls and records is an example of change that must be accommodated by the regulations.

CGMP OBJECTIVES

The objective of the CGMP provision in the law is to require adherence to a current general standard of manufacturing which will promote products that meet intended specifications. Put another way, that the practices employed — including controls — can be expected to result in medicated feed products containing the correct drug at the intended level with proper labeling. Furthermore, that the integrity of the product is maintained, as is the integrity of other products produced in the same facility.

CGMP REGULATIONS—IMPLEMENTATION

The CGMP regulations “formalize” the requirement of adherence to current CGMPs by spelling out specific objectives and the means by which they can be achieved. In some instances, these means — or “how to” — are specific in nature, reflecting the fact that there basically is one way to achieve that objective. In most instances, alternate means are outlined with a provision for utilizing other equally effective means.

An example of specific provisions for mills is to keep feed manufacturing areas and equipment separate from those used for fertilizers, herbicides, insecticides, fungicides, rodenticides and other pesticides” unless approved for use in feed manufacturing. An example of a broader brush approach is the prevention of “unsafe carryover.” Procedures named include “vacuuming, sweeping or washing” and “flushing and/or sequential production of feeds” — and “equally effective procedures.”

LICENSED VERSUS NON-LICENSED CGMPs

The latest revision of the CGMP regulations, sparked by the new FDA “Second Generation” program created two portions applicable to licensed and non-licensed facilities, respectively. As now constructed, the first portion of the regulations, Sections 225.1 through 225.115, applicable to federally licensed mills, consists of a series of two part subsections — parts (a) and (b). Part (a) basically is an expression of philosophy and objectives while part (b) gives a “how to” explanation. The second portion, Sections 225.120 through 225.202, consists of a series of single paragraphs which are expressions of philosophy and objectives paralleling their counterpart subsection (a) of the first portion for licensed mills. With respect to how to comply, non-licensed mills must simply find the best means of achieving the objectives embodied in the expressions of philosophy. In some instances, the “how to” may be comparable to that employed by licensed mills. In other instances, it will be quite different — i.e., simpler. In all cases, compliance practices should be in line with the spirit and intent of good manufacturing practices.

Licensed facilities are subject to routine inspection by or for FDA once every two years for compliance with CGMPs. Non-licensed facilities are not subject to routine FDA inspection. All mills are subject to inspection “for cause,” such as association with adulterated or misbranded feed or food product with illegal drug residues.

On July 21, 1998, the Association of American Feed Control Officials (AAFCO), AFIA and the National Grain & Feed Assn. filed a Citizen Petition with FDA requesting changes to the GGMP regulations.

Specifically, the petitioners asked FDA to merge the two sets of CGMP regulations (licensed and non-licensed or “relaxed”) into one, cohesive set of regulations. For the most part this change, if adopted by FDA, would raise the level of and clarify

the CGMP requirements for non-licensed facilities. The petition is pending.

CGMP INSPECTIONS

FDA issued an inspection guide in June 2001, which is effective for four years. This guide is issued to FDA’s district offices as a “Compliance Program Guide Manual — Feed Manufacturing Compliance Program (2000-2005).” It may be requested from FDA or its district offices and should be reviewed by all feed industry personnel involved in feed regulatory compliance. The current guide is considered an improvement over its predecessor. This new guidance manual incorporates inspections for VFD, BSE feed rule and medicated feed.

The current guide differentiates inspections into surveillance and compliance inspections. Surveillance inspections are those routine, biennial inspections required of all medicated feed application holders. Comprehensive inspections are an in-depth review of a mill’s compliance to CGMPs and normally result when a problem is suspected, previously noted or is apparent.

FEED PRODUCER ACTION

Every feed manufacturer-mixer of medicated feeds must review the portion of CGMP regulations applicable to their operation, determine what constitutes good manufacturing practices for the operation and insure that the practices and procedures followed comply with the spirit and intent of the regulations — and can be considered effective in achieving the intended results.

To aid in interpreting the CGMP regulations, the following comments are offered. They commence with an outline of some basic facts and then address the individual sections of the CGMP regulations.

SOME BASIC FACTS

(1) All producers of medicated feeds are required to follow current good manufacturing regulations.

(2) Depending on the drug sources used to produce medicated feeds, all producers of medicated feeds are divided into two groups — (a) those who must register with FDA and obtain a license and (b) those who are not required to register. This division determines which portion of the CGMP regulations must be observed.

(3) Drugs are divided into two categories — Category I and Category II. Category I drugs require no withdrawal before animals are marketed. Category II drugs have a withdrawal associated with their use or require special consideration.

(4) Drug sources are divided into two types — Type A medicated articles and Type B medicated feeds. Type A products are comparable to standardized drug premixes. Type B products are comparable to feed concentrates or supplements. As such, Type B feed covers a wide range of drug potencies. Type B products are intended for mixing purposes.

NOTE: The third type product — Type C feeds — are complete or free-choice products not intended for mixing.

(5) Any medicated feed producer using one or more Category II, Type A drug sources must register with FDA, obtain a license and is subject to the more detailed CGMP regulations, Sections 225.1 through 225.115. The use of these drug sources requires an approved medicated feed license. Registered facilities are subject to inspection by FDA or FDA agents on a biennial basis for compliance.

The requirement for registration and approved licenses applies to all classes of feed producers — commercial, local dealer-mixers, integrated operations and on-farm mixers. There are no exceptions if one uses one or more Category II Type A drug sources. The dual requirement also applies to anyone producing a medicated free-choice feed — regardless of the drug or its source. This fact is not well understood.

(6) Medicated feed producers using only Category I drugs, regardless of type source and/or Type B Category II drug sources, are not required to register with FDA or obtain a license. As non-registrants, they are subject to the less detailed CGMP regulations — Sections 225.120 through 225.202. Non-registered facilities are not subject to routine FDA inspection. They may be inspected for cause or by state officials.

(7) Federal law prohibits veterinarians from prescribing animal drugs for feeds. No one, including a veterinarian may exceed the limits of the approved animal drug in federal regulations, mix approved animal drugs in feeds for animals not listed in the federal regulation for the particular drug or for a different production class not listed in the regulation. Currently, all approved animal drugs permitted for use in feed are available over-the-counter and do not require a prescription. However, one approved drug requires a veterinary feed directive (VFD).

COMMENTS ON CGMP REGULATIONS

The following comments on each section of the CGMP regulations are provided to aid in review of the regulations:

CGMPs FOR LICENSED MILLS

Section 225.1 — Current good manufacturing practice

Comment: Subsections (a) and (b) provide a capsule summary of background and purpose of the CGMP regulations.

Section 225.10 — Personnel

Comment: The shortest but most important section of the CGMP regulations. A team of qualified individuals with appropriate direction and supervision is the key element for any successful operation. Direction includes written instructions and supervision includes assurance of familiarity with those instructions. Focus is on training, experience and supervision.

Section 225.20 — Buildings

Comment: Appropriate facilities which are capable of their intended purpose of feed production coupled with good interior and exterior housekeeping. Housekeeping aids in preventing pest and insect infestation and in preventing contamination of all kinds. Focus is on appropriate facilities and good housekeeping are required.

Section 225.30 — Equipment

Comment: Similar to “Buildings,” equipment must be capable of intended purpose and well maintained. Focus is on capable equipment and good maintenance.

NOTE: One specific item under equipment is the stipulation to test scales and metering devices at least once per year.

Section 225.35 — Use of work areas, equipment and storage areas for other manufacturing and storage purpose

Comment: To preclude contamination of feed by such materials, fertilizer, herbicides and pesticides must be kept out of feed facilities and equipment. Focus is on prevention of contamination by physical separation.

Section 225.42 — Components

Comment: Components refers to drug sources. A comprehensive approach to administrative quality control over drug components is outlined. It begins with screening upon receipt and the establishment of a record-keeping system that provides continuing drug identity and a complete history from receipt through use of the drug component to produce medicated feed. The heart of this control system is the maintenance of a book drug inventory, a periodic timely comparison of that inventory with the actual physical inventory and immediate appropriate action should there be significant difference. Inherent in this system is the use of drug sources on a first-received, first-used basis. This overall scheme is the primary control, because it provides a continuous contemporaneous type control. Focus is on drug identification, protection and control with quick reaction when controls indicate possible problems. Records can be a series of interrelated records — i.e., they need not take the form of a single

comprehensive record. They should permit the tracing of a given lot of drug from point of receipt through use of that drug.

Section 225.58 — Laboratory controls

Comment: This section complements the foregoing section on “book” controls. Assays are spot checks on these primary controls. The assay requirement is specific. The first batch of feed produced under an approved license is to be sampled and analyzed. Thereafter, three random samples and analyses are to be conducted per year. If the medication is a combination of drugs, only one need be analyzed each time with a rotation of drugs analyzed.

Any out of tolerance assays must be followed up with an investigation as to cause and any needed corrective action taken. Document the investigation and action taken. If deemed necessary, distribution of feed analyzed should be discontinued. The inherent lag between sampling and analytical results and the normal quick use of feed often makes this action moot.

To what extent an out of tolerance assay result needs to be investigated is an unresolved issue often arising in the course of mill inspections. Certainly there is a need to immediately review all pertinent records, check on probable causes, make a determination and take appropriate action. The investigation should be thorough, the action taken in line with the circumstances — and a complete record made for future reference.

NOTE: The assay procedures for some drugs are not considered reliable and problems with good methods occasionally surface. If recurring problems are encountered, it is suggested a separate “problem” file be established and the help of the drug manufacturer be requested. Remember, assays by state feed control officials are accepted by FDA. However, the tolerances established by FDA for each drug are not necessarily in agreement with the analytical variations adopted by AAFCO for each drug. Thus, if a drug assay is considered within tolerance by a state, it may be out-of-tolerance by the FDA (e.g., bacitracin AAFCO AV=40%, FDA tolerance=30%). Check the tolerances established for each drug listed on the medicated feed application.

Section 225.65 — Equipment cleanout procedures

Comment: The twin primary goals of the CGMP regulations are medicated feeds proper in all respects and the protection of the integrity of all other medicated and non-medicated feeds. Equipment cleanout addresses this second goal. The thrust is to minimize and control carryover of a drug into subsequent production — i.e., prevent unsafe carryover. That carryover exists as a recognized fact, as is the need to control it. A number of control procedures are outlined. The most common control utilized is to schedule production with an appropriate sequence that directs carryover to a safe haven. Sequencing should be on a predetermined basis. Practicality points to a system of priorities based on the inherent nature of drugs and feed types, with absolute prohibitions where needed. For example, common sense dictates a complete swine finishing feed should not follow a sulfa-containing feed, that the two feeds should be separated as much as possible by other production. The same is true of monensin-containing feeds and horse feeds and of lincomycin and rabbit feeds.

Again, the goal is to prevent unsafe carryover by utilizing all reasonable, practical means. While the means should be defensible, the actual burden of proving unsafe carryover rests with FDA.

Unsafe carryover is not specifically defined. Unfortunately, information is sparse on the effect of trace amounts of an animal drug in a non-target animal feed. There is some, particularly where the effect can be drastic, as mentioned above. For the most part, common sense must be exercised in setting up a sequencing procedure and priorities as to first and subsequent preferences of order of feed production. For example, it makes sense to group the production of similarly medicated feeds when this is possible and to do so — again, when possible — in order of

decreasing potency. It also makes sense to follow such production with feed for an animal for which the drug is approved — and preferably a concentrate or supplement form of feed which will be further diluted. This might be construed a first priority approach. The practical realities of feed manufacturing dictate the necessity of having other alternatives available.

NOTE: Sequencing and drug carryover are well covered in two FDA compliance policy guides entitled, “Unsafe Contamination of Animal Feed from Drug Carryover” (CPG 680.500) and “Sequencing as a Means to Prevent Unsafe Drug Contamination in the Production, Storage and Distribution of Feeds” (CPG 680.600). Both of these short publications are available from any FDA district office or FDA headquarters.

Section 225.80 — Labeling

Comment: Correct labeling is a must. All appropriate steps must be taken to insure labels are correct when printed, are current when used and accompany the right feed at all times. Standard procedure should require immediate disposal of all outdated feed labels to prevent mislabeling accidents.

Section 225.102 — Master record file and production records

Comment: This is the longest section of the CGMP regulations but one having a single, simple objective — a complete and meaningful history of medicated feed production. That history running from formulation to the point of distribution.

Two points bear mention. First, the master record file is not necessarily a comprehensive single file. It can be and usually is a collection of files — formulation, manufacturing instructions and controls imposed. As such, these files may be rightfully located in different areas of the establishment. Second, all records should carry the identification of the person responsible for them. This is usually accomplished by signing or initialling. Only by knowing who to question can questions be answered. This accountability factor applies to all records.

In the case of computerized records or transmissions from a central office, initialling or signing may be a practical impossibility and some other form of accountability will need to be devised.

Section 225.110 — Distribution records

Comment: The records required are the normal business records of product distribution. Coupled with label codes and operation on a first-made, first-shipped basis, they should enable product to be traced to the field and product in the field to be traced back through the system. This capability is needed to facilitate recall or investigate the cause of field problems.

Section 225.115 — Complaint files

Comment: This section requires a record be maintained of each medicated feed complaint and the action taken on the complaint. This applies to written and oral complaints about the feed attributable to its drug content. Such complaint records are usually held in a separate file apart from non-drug oriented complaints. The record should document the evaluation of the complaint and action taken, which is good business practice and a measure of protection in the event of any future regulatory or legal action. Since feed manufacturers are not drug experts, it is appropriate to involve the drug manufacturer who can more accurately evaluate questions of safety and effectiveness — and make any necessary reports to FDA.

CGMP SECTIONS FOR NON-LICENSED FACILITIES

NOTE: FDA, with industry input, published a straightforward booklet, “CGMPs for Medicated Feed Manufacturers Not Required to Register with FDA” — CVM Guideline 72. It can be obtained from, CVM-FDA, 7500 Standish Place, Rockville, Md. 20855; (301) 827-6651. The following comments parallel

the contents of that publication.

Section 225.120 — Buildings and grounds

Comment: Emphasis parallels that of Section 225.20 — i.e., suitable buildings and good interior and exterior housekeeping.

Section 225.130 — Equipment

Comment: Equipment must be capable of intended function and adequately maintained in a clean and orderly fashion.

Section 225.135 — Work and storage areas

Comment: Tracks Section 225.35 in specifying exclusion of fertilizers, herbicides and pesticides from feed areas and equipment to preclude contamination.

Section 225.142 — Components

Comment: Requires procedures to identify, protect and control the use of drug sources — both Type A and Type B sources. Reference is made to “inventory control” on the receipt and use of drug sources. While specifics are not given, a form of inventory control similar to that described in Section 225.42 should be considered in the interests of good business practice. There is a specific requirement that all drug sources be used in conformance with label directions. Focus is on identification, protection, control and conformance with directions for use.

Section 225.158 — Laboratory assays

Comment: No assays of medicated feeds are required. However, if assays are performed, including assays by state control officials, with results outside accepted limits, there must be an appropriate investigation and any necessary corrective action. Focus is on reaction to indication of a possible problem.

Again, assays by state feed control officials are accepted by FDA. However, the tolerances established by FDA for each drug are not necessarily in agreement with the analytical variations (AV) adopted by AAFCO for each drug. Thus, if a drug assay is considered within tolerance by a state, it may be out-of-tolerance by the FDA (e.g., bacitracin AAFCO AV=40%, FDA tolerance=30%). Check the tolerances established for each drug listed on the MFA.

Section 225.165 — Equipment cleanout procedures

Comment: This is the shortest section, but a vital one, applicable to non-licensed mills. Complete focus is on preventing unsafe carryover.

Section 225.180 — Labeling

Comment: Label controls must result in correct and complete labels and the correct matching of labels and feeds. Focus is on labeling correct in all respects.

Section 225.202 — Records

Comment: Records must provide a history of formulation, production and distribution and be adequate for recall purposes. Focus is on a documented record and recall capacity.

CONCLUSION

Good manufacturing practices are synonymous with good business practices. CGMP regulation emphasis is on good housekeeping, predetermined systematic procedures, effective controls and records providing a meaningful history of the operation. CGMPs are founded in past experience, but must be ever subject to modification or fine tuning in light of recent experience and new information.

Good manufacturing practices, their determination and how to comply, are fluid subjects requiring a continuing exchange of information, viewpoints and ideas. Enforcement through mill inspections often reveals shades of difference between the feed industry and FDA. The ongoing resolution of these differences on what constitutes a good manufacturing practice is a must that there is common understanding. ■

Text of the Food & Drug Administration's Current Good Manufacturing Practice Regulations For Feeds

EDITOR'S NOTE: Below is the text of the Food & Drug Administration's Good Manufacturing Practices. These CGMPs were published by FDA in the Nov. 30, 1976, Federal Register and were revised in the March 3, 1986, and Nov. 19, 1999, Federal Register.

PART 210 — CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING, PROCESSING, PACKING OR HOLDING OF DRUGS; GENERAL

Part 210 is amended by revising the part heading as set out above.

In § 210.3 by revising paragraph (b)(13) and (14), to read as follows:

§ 210.3 Definitions

(b)***

(13) The term "medicated feed" means any Type B or Type C medicated feed as defined in § 558.3 of this chapter. The feed contains one or more drugs as defined in section 201(g) of the act. The manufacture of medicated feeds is subject to the requirements of Part 225 of this chapter.

(14) The term "medicated premix" means a Type A medicated article as defined in § 558.3 of this chapter. The article contains one or more drugs as defined in section 201(g) of the act. The manufacture of medicated premixes is subject to the requirements of Part 226 of this chapter.

PART 225 — CURRENT GOOD MANUFACTURING PRACTICE FOR MEDICATED FEEDS

Subpart A — General Provisions

225.1 Current good manufacturing practice
225.10 Personnel

Subpart B — Construction and Maintenance of Facilities and Equipment

225.20 Buildings
225.30 Equipment
225.35 Use of work areas, equipment and storage areas for other manufacturing and storage purposes

Subpart C — Product Quality Control

225.42 Components
225.58 Laboratory controls
225.65 Equipment clean-out procedures
Subpart D — Packaging and Labeling
225.80 Labeling

Subpart E — Records and Reports

225.102 Master record file and production records
225.110 Distribution records
225.115 Complaint files

Subpart F — Facilities and Equipment

225.120 Building and grounds
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225.135 Work and storage areas

Subpart G — Product Quality Assurance

225.142 Components
225.158 Laboratory assays
225.165 Equipment cleanout procedures

Subpart H — Labeling

225.180 Labeling
Subpart I — Records
225.202 Formula, production and distribution records

Subpart A — General Provisions

§ 225.1 Current good manufacturing practice

(a) Section 501 (a) (2) (B) of the Federal Food, Drug & Cosmetic Act provides that a drug (including a drug contained in a medicated feed) shall be deemed to be adulterated if the methods used in or the facilities or controls used for its manufacture, processing, packing or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirement of the act as to safety and has the identity and strength and meets the quality and purity characteristics, which it purports or is represented to possess.

(b)(1) The provisions of this part set forth the criteria for determining whether the manufacture of a medicated feed is in compliance with current good manufacturing practice. These regulations shall apply to all types of facilities and equipment used in the production of medicated feeds and they shall also govern those instances in which failure to adhere to the

regulations has caused nonmedicated feeds that are manufactured, processed, packed or held to be adulterated. In such cases, the medicated feed shall be deemed to be adulterated within the meaning of section 501(a)(2)(B) of the act and the nonmedicated feed shall be deemed to be adulterated within the meaning of section 402(a)(2)(D) of the act.

(2) The regulations in § 225.10 through 225.115 apply to facilities manufacturing one or more medicated feeds for which an approved medicated feed application is required. The regulations in § 225.120 through 225.202 apply to facilities manufacturing solely medicated feeds for which an approved license is not required.

(c) In addition to the recordkeeping requirements in this part, Type B and Type C medicated feeds made from Type A articles or Type B feeds under approved NADA's and a medicated feed mill license are subject to the requirements of Sec. 510.301 of this chapter.

§ 225.10 Personnel

(a) Qualified personnel and adequate personnel training and supervision are essential for the proper formulation, manufacture and control of medicated feeds. Training and experience lead to proper use of equipment, maintenance of accurate records and detection and prevention of possible deviations from current good manufacturing practices.

(b)(1) All employees involved in the manufacture of medicated feeds shall have an understanding of the manufacturing or control operation(s) which they perform, including the location and proper use of equipment.

(2) The manufacturer shall provide an on-going program of evaluation and supervision of employees in the manufacture of medicated feeds.

Subpart B — Construction and Maintenance of Facilities and Equipment

§ 225.20 Buildings

(a) The location, design, construction and physical size of the buildings and other production facilities are factors

important to the manufacture of medicated feed. The features of facilities necessary for the proper manufacture of medicated feed include provision for ease of access to structures and equipment in need of routine maintenance; ease of cleaning of equipment and work areas; facilities to promote personnel hygiene; structural conditions for control and prevention of vermin and pest infestation; adequate space for the orderly receipt and storage of drugs and feed ingredients and the controlled flow of these materials through the processing and manufacturing operations and the equipment for the accurate packaging, and delivery of a medicated feed of specified labeling and composition.

(b) The construction and maintenance of buildings in which medicated feeds are manufactured, processed, packaged, labeled or held shall conform to the following:

(1) The building grounds shall be adequately drained and routinely maintained so that they are reasonably free from litter, waste, refuse, uncut weeds or grass, standing water and improperly stored equipment.

(2) The building(s) shall be maintained in a reasonably clean and orderly manner.

(3) The building(s) shall be of suitable construction to minimize access by rodents, birds, insects and other pests.

(4) The buildings shall provide adequate space and lighting for the proper performance of the following medicated feed manufacturing operations:

(i) The receipt, control and storage of components.

(ii) Component processing.

(iii) Medicated feed manufacturing.

(iv) Packaging and labeling.

(v) Storage of containers, packaging materials, labeling and finished products.

(vi) Routine maintenance of equipment.

§ 225.30 Equipment

(a) Equipment which is designed to perform its intended function and is properly installed and used is essential to the manufacture of medicated feeds. Such equipment permits production of feeds of uniform quality, facilitates cleaning and minimizes spillage of drug components and finished product.

(b) (1) All equipment shall possess the capability to produce a medicated feed of intended potency, safety and purity.

(2) All equipment shall be maintained in a reasonably clean and orderly manner.

(3) All equipment, including scales and liquid metering devices, shall be of suitable size, design, construction, precision and accuracy for its intended purpose.

(4) All scales and metering devices shall be tested for accuracy upon installation and at least once a year thereafter or more frequently as may be necessary to insure their accuracy.

(5) All equipment shall be so constructed and maintained as to prevent lubricants and coolants from becoming unsafe additives in feed components or medicated feed.

(6) All equipment shall be designed, constructed, installed and maintained so as to facilitate inspection and use of cleanout procedure(s).

§ 225.35 Use of work areas, equipment and storage areas for other manufacturing and storage purpose

(a) Many manufacturers of medicated feeds are also involved in the manufacture, storage or handling of products which are not intended for animal feed use, such as fertilizers, herbicides, insecticides, fungicides, rodenticides and other pesticides. Manufacturing, storage or handling of nonfeed and feed products in the same facilities may cause adulteration of feed products with toxic or otherwise unapproved feed additives.

(b) Work areas and equipment used for the manufacture or storage of medicated feeds or components thereof shall not be used for and shall be physically separated from, work areas and equipment used for the manufacture of fertilizers, herbicides, insecticides, fungicides, rodenticides and other pesticides unless such articles are approved drugs or approved food additives intended for use in the manufacture of medicated feed.

Subpart C — Product Quality Control § 225.42 Components

(a) A medicated feed, in addition to providing nutrients, is a vehicle for the administration of a drug, or drugs, to animals. To ensure proper safety and effectiveness, such medicated feeds must contain the labeled amounts of drugs. It is necessary that adequate procedures be established for the receipt, storage and inventory control for all such drugs to aid in assuring their identity, strength, quality and purity when incorporated into products.

(b) The receipt, storage and inventory of drugs, including undiluted drug components, medicated premixes and semiprocessed (i.e., intermediate premixes, in-plant premixes and concentrates) intermediate mixes containing drugs, which are used in the manufacture and processing of medicated feeds, shall conform to the following:

(1) Incoming shipments of drugs shall be visually examined for identity and damage. Drugs which have been subjected to conditions which may have

adversely affected their identity, strength, quality or purity shall not be accepted for use.

(2) Packaged drugs in the storage areas shall be stored in their original closed containers.

(3) Bulk drugs shall be identified and stored in a manner such that their identity, strength, quality and purity will be maintained.

(4) Drugs in the mixing areas shall be properly identified, stored, handled and controlled to maintain their integrity and identity. Sufficient space shall be provided for the location of each drug.

(5) A receipt record shall be prepared and maintained for each lot of drug received. The receipt record shall accurately indicate the identity and quantity of the drug, the name of the supplier, the supplier's lot number or an identifying number assigned by the feed manufacturer upon receipt which relates to the particular shipment, the date of receipt the condition of the drug when received and the return of any damaged drugs.

(6) A daily inventory record for each drug used shall be maintained and shall list by manufacturer's lot number or the feed manufacturer's shipment identification number at least the following information:

(i) The quantity of drugs on hand at the beginning and end of the work day (the beginning amount being the same as the previous day's closing inventory if this amount has been established to be correct); the quantity shall be determined by weighing, counting or measuring, as appropriate.

(ii) The amount of each drug used sold or otherwise disposed of.

(iii) The batches or production runs of medicated feed in which each drug was used.

(iv) When the drug is used in the preparation of a semiprocessed intermediate mix intended for use in the manufacture of medicated feed, any additional information which may be required for the purpose of paragraph (b) (7) of this section.

(v) Action taken to reconcile any discrepancies in the daily inventory record.

(7) Drug inventory shall be maintained for each lot or shipment of drug by means of a daily comparison of the actual amount of drug used with the theoretical drug usage in terms of the semiprocessed, intermediate and finished medicated feeds manufactured. Any significant discrepancy shall be investigated and corrective action taken. The medicated feed(s) remaining on the premises which are affected by this discrepancy shall be detained until the discrepancy is reconciled.

(8) All records required by this section shall be maintained on the premises for at least one year after complete use of a drug component of a specific lot number or feed manufacturer's shipment identification number.

§ 225.58 Laboratory controls

(a) The periodic assay of medicated feeds for drug components provides a measure of performance of the manufacturing process in manufacturing a uniform product of intended potency.

(b) The following assay requirements shall apply to medicated feeds:

(1) For feeds requiring a medicated feed mill license (Form FDA 3488) for their manufacture and marketing, at least three representative samples of medicated feed containing each drug or drug combination used in the establishment shall be collected and assayed by approved official methods, at periodic intervals during the calendar year, unless otherwise specified in this chapter. At least one of these assays shall be performed on the first batch using the drug. If a medicated feed contains a combination of drugs, only one of the drugs need be subject to analysis each time, provided the one tested is different from the one(s) previously tested.

(2) (Reserved)

(c) The originals or copies of all results of assays, including those from state feed control officials and any other governmental agency, shall be maintained on the premises for a period of not less than one year after distribution of the medicated feed. The results of assays performed by state feed control officials may be considered toward fulfillment of the periodic assay requirements of this section.

(d) Where the results of assays indicate that the medicated feed is not in accord with label specifications or is not within permissible assay limits as specified in this chapter, investigation and corrective action shall be implemented and an original or copy of the record of such action maintained on the premises.

(e) Corrective action shall include provisions for discontinuing distribution where the medicated feed fails to meet the labeled drug potency. Distribution of subsequent production of the particular feed shall not begin until it has been determined that proper control procedures have been established.

§ 225.65 Equipment cleanout procedures

(a) Adequate cleanout procedures for all equipment used in the manufacture and distribution of medicated feeds are essential to maintain proper drug potency and avoid unsafe contamination of feeds with drugs. Such procedures may

consist of cleaning by physical means; e.g., vacuuming, sweeping, washing. Alternatively, flushing or sequencing or other equally effective techniques may be used whereby the equipment is cleaned either through use of a feed containing the same drug(s) or through use of drug-free feedstuffs.

(b) All equipment, including that used for storage, processing, mixing, conveying and distribution that comes in contact with the active drug component feeds in process or finished medicated feed shall be subject to all reasonable and effective procedures to prevent unsafe contamination of manufactured feed. The steps used to prevent unsafe contamination of feeds shall include one or more of the following or other equally effective procedures:

(1) Such procedures shall, where appropriate, consist of physical means (vacuuming, sweeping or washing), flushing and/or sequential production of feeds.

(2) If flushing is utilized, the flush material shall be properly identified, stored and used in a manner to prevent unsafe contamination of other feeds.

(3) If sequential production of medicated feeds is utilized, it shall be on a predetermined basis designed to prevent unsafe contamination of feeds with residual drugs.

Subpart D — Packaging and Labeling § 225.80 Labeling

(a) Appropriate labeling identifies the medicated feed and provides the user with directions for use which, if adhered to, will assure that the article is safe and effective for its intended purposes.

(b) (1) Labels and labeling, including placards, shall be received, handled and stored in a manner that prevents labeling mix-ups and assures that correct labeling is employed for the medicated feed.

(b) (2) Labels and labeling, including placards, upon receipt from the printer shall be proofread against the master record file to verify their suitability and accuracy. The proofread label shall be dated, initialed by the responsible individual and kept for one year after all the labels from that batch have been used.

(3) In those instances where medicated feeds are distributed in bulk, complete labeling shall accompany the shipment and be supplied to the consignee at the time of delivery. Such labeling may consist of a placard or other labels attached to the invoice or delivery ticket or manufacturer's invoice that identifies the medicated feed and includes adequate information for the safe and effective use of the medicated feed.

(4) Label stock shall be reviewed periodically and discontinued labels shall be

discarded.

Subpart E — Records and Reports § 225.102 Master record file and production records

(a) The master record file provides the complete procedure for manufacturing a specific product, setting forth the formulation, theoretical yield, manufacturing procedures, assay requirement(s) and labeling of batches or production runs. The production record(s) include(s) the complete history of a batch or production run. This record includes the amounts of drugs used, the amount of medicated feed manufactured and provides a check for the daily inventory record of drug components.

(b) The master record file and production records shall comply with the following provisions:

(1) A master record file shall be prepared, checked, dated and signed or initialed by a qualified person and shall be retained for not less than one year after production of the last batch or production run of medicated feed to which it pertains. The master record file or card shall include at least the following:

(i) The name of the medicated feed.

(ii) The name and weight percentage or measure of each drug or drug combination and each nondrug ingredient to be used in manufacturing a stated weight of the medicated feed.

(iii) A copy or description of the label or labeling that will accompany the medicated feed.

(iv) Manufacturing instructions or reference thereto that have been determined to yield a properly mixed medicated feed of the specified formula for each medicated feed produced on a batch or continuous operation basis, including mixing steps, mixing times and, in the case of medicated feeds produced by continuous production run, any additional manufacturing directions including, when indicated, the setting of equipment.

(v) Appropriate control directions or reference thereto, including the manner and frequency of collecting the required number of samples for specified laboratory assay.

(2) The original production record or copy thereof shall be prepared by qualified personnel for each batch or run of medicated feed produced and shall be retained on the premises for not less than one year. The production record shall include at least the following:

(i) Product identification, date of production and a written endorsement in the form of a signature or initials by a responsible individual.

(ii) The quantity and name of drug components used.

(iii) The theoretical quantity of medicated feed to be produced.

(iv) The actual quantity of medicated feed produced. In those instances where the finished feed is stored in bulk and actual yield cannot be accurately determined, the firm shall estimate the quantity produced and provide the basis for such estimate in the master record file.

(3) In the case of a custom formula feed made to the specifications of a customer, the master record file and production records required by this section shall consist either of such records or of copies of the customer's purchase orders and the manufacturer's invoices bearing the information required by this section. When a custom order is received by telephone, the manufacturer shall prepare the required production records.

(4) Batch production records shall be checked by a responsible individual at the end of the working day in which the product was manufactured to determine whether all required production steps have been performed. If significant discrepancies are noted, an investigation shall be instituted immediately and the production record shall describe the corrective action taken.

(5) Each batch or production run of medicated feed shall be identified with its own individual batch or production run number, code, date or other suitable identification applied to the label, package, invoice or shipping document. This identification shall permit the tracing of the complete and accurate manufacturing history of the product by the manufacturer.

§ 225.110 Distribution records

(a) Distribution records permit the manufacturer to relate complaints to specific batches and/or production runs of medicated feed. This information may be helpful in instituting a recall.

(b) Distribution records for each shipment of a medicated feed shall comply with the following provisions:

(1) Each distribution record shall include the date of shipment, the name and address of purchaser, the quantity shipped and the name of the medicated feed. A lot or control number or date of manufacture or other suitable identification shall appear on the distribution record or the label issued with each shipment.

(2) The originals or copies of the distribution records shall be retained on the premises for not less than one year after the date of shipment of the medicated feed.

§ 225.115 Complaint files

(a) Complaints and reports of experiences of product defects relative to the drug's efficacy or safety may provide an indicator as to whether or not medicated feeds have been manufactured in confor-

mity with current good manufacturing practices. These complaints and experiences may reveal the existence of manufacturing problems not otherwise detected through the normal quality control procedures. Timely and appropriate follow-up action can serve to correct a problem and minimize future problems.

(b) The medicated feed manufacturer shall maintain on the premises a file which contains the following information:

(1) The original or copy of a record of each oral and written complaint received relating to the safety and effectiveness of the product produced. The record shall include the date of the complaint, the complainant's name and address, name and lot or control number or date of manufacture of the medicated feed involved and the specific details of the complaint. This record shall also include all correspondence from the complainant and/or memoranda of conversations with the complainant and a description of all investigations made by the manufacturer and of the method of disposition of the complaint.

(2) For medicated feeds whose manufacture require a medicated feed mill license (Form FDA 3448), records and reports of clinical and other experience with the drug shall be maintained and reported, under Sec. 510.301 of this chapter.

Subpart F — Facilities and Equipment § 225.120 Buildings and grounds

Buildings used for production of medicated feed shall provide adequate space for equipment, processing and orderly receipt and storage of medicated feed. Areas shall include access for routine maintenance and cleaning of equipment. Buildings and grounds shall be constructed and maintained in a manner to minimize vermin and pest infestation.

§ 225.130 Equipment

Equipment shall be capable of producing a medicated feed of intended potency and purity and shall be maintained in a reasonably clean and orderly manner. Scales and liquid metering devices shall be accurate and of suitable size, design, construction, precision and accuracy for their intended purposes. All equipment shall be designed, constructed, installed and maintained so as to facilitate inspection and use of cleanout procedure(s).

§ 225.135 Work and storage areas

Work areas and equipment used for the production or storage of medicated feeds or components thereof shall not be used for and shall be physically separated from, work areas and equipment used for the manufacture and storage of fertilizers, herbicides, insecticides, fungicides, rodenticides and other pesticides unless such articles are approved for use in the

manufacture of animal feed.

Subpart G — Product Quality Assurance § 225.142 Components

Adequate procedures shall be established and maintained for the identification, storage and inventory control (receipt and use) of all Type A medicated articles and Type B medicated feeds intended for use in the manufacture of medicated feeds to aid in assuring the identity, strength, quality and purity of these drug sources. Packaged Type A medicated articles and Type B medicated feeds shall be stored in designated areas in their original closed containers. Bulk Type A medicated articles and bulk Type B medicated feeds shall be identified and stored in a manner such that their identity, strength, quality and purity will be maintained. All Type A medicated articles and Type B medicated feeds shall be used in accordance with their labeled mixing directions.

§ 225.158 Laboratory assays

Where the results of laboratory assays of drug components, including assays by state feed control officials, indicate that the medicated feed is not in accord with the permissible limits specified in this chapter, investigation and corrective action shall be implemented immediately by the firm and such records shall be maintained on the premises for a period of one year.

§ 225.165 Equipment cleanout procedures

Adequate procedures shall be established and used for all equipment used in the production and distribution of medicated feeds to avoid unsafe contamination of medicated and nonmedicated feeds.

Subpart H — Labeling

§ 225.180 Labeling

Labels shall be received, handled and stored in a manner that prevents label mix-ups and assures that the correct labels are used for the medicated feed. All deliveries of medicated feeds, whether bagged or in bulk, shall be adequately labeled to assure that the feed can be properly used.

Subpart I — Records

§ 225.202 Formula, production and distribution records

Records shall be maintained identifying the formulation, date of mixing and if not for own use, date of shipment. The records shall be adequate to facilitate the recall of specific batches of medicated feed that have been distributed. Such records shall be retained on the premises for one year following the date of last distribution. ■

Part III: ■ Forms

Please note: These forms have been slightly reduced in size to fit. Full-size forms are available on the CD as separate files: FDA-3448.pdf and FDA-2656.pdf.

Form FDA-2656.pdf is an interactive form that can be submitted electronically to the FDA (see instructions on form).

DEPARTMENT OF HEALTH AND HUMAN SERVICES Food and Drug Administration MEDICATED FEED MILL LICENSE APPLICATION		Form Approved: OMB No. 0910-0337 Expiration Date: December 31, 2006 See OMB Statement on Reverse	
		FOR FDA USE ONLY	
		Approval Date: _____	
		Signed by: _____ <i>(For the Commissioner of Food and Drugs)</i>	
MANUFACTURING SITE LEGAL BUSINESS NAME:		PHONE NUMBER: ()	
ADDRESS: <i>(Street, City, State and Zip code)</i>		EXT.	
		FAX NUMBER: ()	
MAILING ADDRESS / PHONE NUMBERS: <i>(if different from above)</i>	TYPE OF APPLICATION:	FDA REGISTRATION NUMBER:	LICENSE NUMBER:
Phone number: ()	<input type="checkbox"/> Original Application	_____	_____
FAX number: ()	<input type="checkbox"/> Resubmission of Application		
	<input type="checkbox"/> Supplemental Application		
As a Medicated Feed Mill Licensee, you have certified that: <ul style="list-style-type: none"> Animal feeds bearing or containing new animal drugs are manufactured and labeled in accordance with the applicable regulations published pursuant to section 512(i) of the Federal Food, Drug and Cosmetic Act (the Act). The methods used in, and the facilities and controls used for, manufacturing, processing, packaging, and holding such animal feeds are in conformity with current good manufacturing practice as described in section 501(9a)(2)(B) of the Act and 21 CFR 225. Your manufacturing facility will establish and maintain all records required by regulation or order issued under sections 512 (m)(4)(B)(i) and 504 (a)(3)(A) of the Act, and will permit access to, or copying or verification of such records by FDA. 			
As a Medicated Feed Mill Licensee, you have committed to: <ul style="list-style-type: none"> Possessing current approved Type B and C Medicated Feed labeling for each animal drug in animal feed prior to receiving the Type A Medicated Article Containing such drug. Renewing registration each year with the FDA as required by 21 CFR 207.20 and 21 CFR 207.21. Using only non-drug feed components recognized in the Association of American Feed Control Officials (AAFCO) Official Publication or sanctioned by FDA under 21 CFR 573, 582 and 584 as suitable for use in animal feeds. Supplementing your license application when changes in ownership or address occur. Supplements are to be sent promptly to the Division of Animal Feeds, CVM, FDA, 7500 Standish Place, Rockville, Maryland 20855. Complying with all other applicable provisions of the Act. 			
I CERTIFY that all of the statements made in this application are true and complete to the best of my knowledge and ability. WARNING: A willfully false certification is a criminal offense. U.S. Code, Title 18, Sec. 1001.			
NAME OF THE MOST RESPONSIBLE INDIVIDUAL FOR THIS MANUFACTURING SITE:		TITLE OF MOST RESPONSIBLE INDIVIDUAL:	
SIGNATURE OF THE MOST RESPONSIBLE INDIVIDUAL: <i>(Application must be signed and dated)</i>		DATE:	

Public reporting burden for this collection of information is estimated to average 15 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS Reports Clearance Officer
Paperwork Reduction Project 0910-0337
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please DO NOT RETURN this application to this address.

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service FOOD AND DRUG ADMINISTRATION REGISTRATION OF DRUG ESTABLISHMENT/ LABELER CODE ASSIGNMENT (In accordance with Public Law 92-387)		FDA USE ONLY	FDA USE ONLY
NOTICE: This report is required by law (21 C.F.R. 207.20). Failure to report can result in imprisonment for not more than one year or a fine of not more than \$1,000, or both. (FD&C Act, Section 303).		LABELER CODE	REGISTRATION NUMBER
SECTION A - SITE INFORMATION			
REPORTING FIRM NAME			STATE OF INC.
SITE ADDRESS (No P.O. Box)			SITE TELEPHONE NUMBER ()
CITY	STATE	ZIP CODE	COUNTRY
SITE MAILING ADDRESS (If different from site address)			BUSINESS CATEGORY: <input type="checkbox"/> HUMAN <input type="checkbox"/> VETERINARY
CITY	STATE	ZIP CODE	COUNTRY
DOING BUSINESS AS (DBA) NAME OF FIRM (if applicable)			SITE INTERNET/EMAIL ADDRESS
PARENT COMPANY NAME			
REASON(S) FOR SUBMISSION <input type="checkbox"/> Firm Registration <input type="checkbox"/> Registration of Additional Site <input type="checkbox"/> Re-Registration <input type="checkbox"/> LC Assignment <input type="checkbox"/> Name Change		TYPE OF OWNERSHIP <input type="checkbox"/> Address Change <input type="checkbox"/> Merger/Buyout <input type="checkbox"/> Reentry into Business with Same Name <input type="checkbox"/> Out of Business <input type="checkbox"/> Sole Proprietorship <input type="checkbox"/> Partnership <input type="checkbox"/> Coop. Assn. <input type="checkbox"/> Corporation <input type="checkbox"/> Other _____	PERSON SUBMITTING DATA AND TELEPHONE BUSINESS TYPE <input type="checkbox"/> Manufacturer <input type="checkbox"/> Repacker <input type="checkbox"/> Relabeler <input type="checkbox"/> Distributor* <input type="checkbox"/> Foreign Country <input type="checkbox"/> Analytical Lab <input type="checkbox"/> Other _____
SECTION B - FIRM COMPLIANCE MAILING ADDRESS for Annual Listing Report and/or Firm Correspondence			
NUMBER AND STREET AND/OR P.O. BOX and ATTENTION LINE and/or Internal Mail Code			TELEPHONE NUMBER ()
CITY	STATE	ZIP CODE	COUNTRY
			COMPLIANCE INTERNET/EMAIL ADDRESS
SECTION C - ADDITIONAL FIRM AND SITE INFORMATION			
NAME OF OWNER, PARTNERS OR OFFICERS		TITLE	POSITION
OTHER FIRMS DOING BUSINESS AT THIS SITE			
LABELER CODE	FIRM NAME	LABELER CODE	FIRM NAME
SECTION D - SIGNATURE			
SIGNATURE OF AUTHORIZING OFFICIAL		TITLE	DATE
*DISTRIBUTOR'S CERTIFICATION: As a, Distributor, I am submitting product listing information to the FDA on my own behalf. I have provided a copy of this certification (Form FDA 2656) to the registered manufacturer(s). My signature and phone number are listed below.		SIGNATURE OF DISTRIBUTOR	
RETURN THIS FORM TO: FOOD AND DRUG ADMINISTRATION INFORMATION MANAGEMENT TEAM, HFD-095 5600 FISHERS LANE ROCKVILLE, MD 20857 INTERNET: DRUGLISTING@CDER.FDA.GOV		DISTRIBUTOR'S TELEPHONE NUMBER ()	

If using Federal Express, DHL or any special carrier to return the forms, please use the following address:

(Please refer to the Drug Registration and Listing Instruction Booklet.)

When completing this form, please refer to the Drug Registration and Listing Instruction Booklet for assistance.
PLEASE PRINT IN ENGLISH USING BLACK INK.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
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Part IV: ■ Regulations

[FR Doc. 00-31277 Filed 12-7-00; 8:45 am]
BILLING CODE 6717-01-M

**DEPARTMENT OF HEALTH AND
HUMAN SERVICES**

Food and Drug Administration

21 CFR Parts 510, 514, and 558

[Docket No. 99N-1591]

**Animal Drug Availability Act;
Veterinary Feed Directive**

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the new animal drug regulations to implement the veterinary feed directive (VFD) drugs section of the Animal Drug Availability Act of 1996 (ADAA). A VFD drug is intended for use in animal feed. Its use is permitted only under the professional supervision of a licensed veterinarian in the course of the veterinarian's professional practice. This new regulation states the requirements for distribution and use of a VFD drug and animal feed containing a VFD drug.

DATES: This rule is effective January 8, 2001.

FOR FURTHER INFORMATION CONTACT: George Graber, Center for Veterinary Medicine (HFV-220), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-827-6651, e-mail: ggraber@cvm.fda.gov.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of July 2, 1999 (64 FR 35966), FDA proposed regulations to establish the requirements relating to distribution and use of VFD drugs and animal feeds containing VFD drugs. We provided 90 days for comment on the proposed rule.

Prior to 1996, we had only two options for regulating the distribution of animal drugs: (1) Over-the-counter (OTC), and (2) prescription. However, we determined that certain new animal drugs, vital to animal health, should be approved for use in animal feed, only if these medicated feeds were administered under a veterinarian's order and professional supervision. For example, veterinarians are needed to control the use of certain antimicrobials. This control is critical to reducing unnecessary use of such drugs in animals and to slowing or preventing

any potential for the development of bacterial resistance to antimicrobial drugs. Safety concerns relating to difficulty of diagnosis of disease conditions, high toxicity, or other reasons may also dictate that the use of a medicated feed be limited to use by order and under the supervision of a licensed veterinarian.

Regulation of animal drugs for use in medicated feeds under traditional prescription systems has proven unworkable. The prescription legend invokes the application of State pharmacy laws. As a practical matter, the application of State pharmacy laws to medicated feeds would burden State pharmacy boards and impose costs on animal feed manufacturers to such an extent that it would be impractical to make these critically needed new animal drugs available for animal therapy.

After considerable deliberation with, and support from, the Coalition for Animal Health, an organization that represents major sectors of animal agriculture, and with support from State regulatory agencies, Congress enacted legislation in 1996 that amended the Federal Food, Drug, and Cosmetic Act (the act) in ways intended to facilitate the approval and marketing of new

animal drugs and medicated feed. This legislation, the ADAA (Public Law 104–250), among other things, established a new class of restricted feed use drugs that may be distributed without invoking State pharmacy laws (21 U.S.C. 354).

Although statutory controls on the use of VFD drugs are similar in some respects to those for prescription animal drugs regulated under section 503(f) of the act (21 U.S.C. 353(f)), the implementing VFD regulations are tailored to the unique circumstances relating to the manufacture and distribution of medicated animal feeds. This final rule will ensure the protection of public health while enabling animal producers to obtain and use needed drugs as efficiently and cost-effectively as possible.

To date, we have approved one VFD drug, tilmicosin, an antimicrobial approved for administration via animal feed for control of swine respiratory diseases (§ 558.618 (21 CFR 558.618)). The current regulation for tilmicosin, at § 558.618(d)(4), specifies required cautionary labeling for the VFD drug and any feed manufactured from the VFD drug and describes the information that the attending veterinarian must provide as part of the VFD. The proposed cautionary labeling in § 558.6(f) was in substance the same as the tilmicosin cautionary labeling but had minor word differences. To assure consistency in cautionary labeling for tilmicosin and any future VFD drugs, we have revised our proposed cautionary labeling in § 558.6(f) to conform to tilmicosin cautionary language in § 558.618(d)(4). Section 558.618(d)(4) is therefore being removed as its provisions are now a part of this final rule at §§ 558.6(a)(4) [content of VFD] and 558.6(f) [cautionary labeling].

II. Comments on the Proposed Rule

We received eight letters commenting on the proposed rule. One was from a feed manufacturer. The balance were from associations representing the veterinary profession, feed manufacturers, the animal health industry, animal producers, and feed control regulators. Generally, the comments were quite supportive of the VFD concept. Significant issues addressed in the comments involved the means of transmission of VFD's, the length of time a VFD would be valid, the appropriateness of refills or reorders, and our proposed automatic classification of VFD drugs as Category II drugs.

Following is our response to comments, grouped by issue:

A. Transmission of VFD's

(Comment 1) All eight comments mentioned this issue. Comments were evenly split, with the veterinary profession, producers, and drug industry desiring maximum use of paper, facsimile, phone, e-mail, and new technology as it develops. The feed industry and feed control regulators opted for paper copy with the possibility of facsimile transmission with proper safeguards. They did not support phone transmission.

Objections to facsimile and other electronic transmission of VFD's were based on a perceived lack of security of transmitted information, difficulty in substantiating authenticity of the VFD, and ability of the client to forward a VFD to multiple distributors. In the case of phone transmission, comments stressed the possibility of fraudulent orders, risk of error in reducing the order to writing, and the burden placed on the manufacturer/distributor to authenticate the VFD order. One comment stated that the oversight by the veterinarian is the underlying reason that Congress created VFD drugs. The comment contended that this oversight is lost when we allow a VFD feed to be distributed in the absence of a signed, original VFD physically present at the distributor at the time of distribution.

Proponents of the use of a wide range of methods for VFD transmission suggest that distribution would be unnecessarily delayed for lack of a written and signed form physically present at the distributor. Two comments suggested that FDA be open to new innovations in electronic transmission such as a web-based server that would require the use of secure user (veterinarian owned) accounts using user-names, passwords, and electronic signatures. We are not opposed to the use of new innovations and technologies. We would not object to a system that can be demonstrated as being in compliance with applicable regulations and practices that govern such systems.

We believe we must accommodate those situations where prompt hand delivery of a VFD is not possible, but immediate delivery of a VFD feed is necessary. To accomplish this, we will allow transmission by facsimile or other electronic means provided safeguards are in place to prevent misuse. The industry must provide assurances that these technologies, as appropriate, are in compliance with part 11 (21 CFR part 11). Using a computer as a web-based server to create, modify, maintain, or transmit required records as well as using electronic signatures for those

records is subject to part 11. It would be up to industry to prove that a system is capable of its intended purpose. Part 11 "applies to all records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted under record requirements in any of the agency's regulations or records submitted to the agency," unless specifically excepted by regulation(s). In order for electronic records to be used in lieu of paper records, they must be in compliance with the provisions stated in § 11.2. These electronic records and signatures, computer systems (including hardware and software), controls, and accompanying documentation must be readily available for and subject to inspection by FDA.

We disagree with the comment that facsimile transmission of the VFD poses a significant problem as the client may reproduce the copy to place multiple orders. While the possibility exists that a client may submit the copy of the VFD to several distributors to obtain additional VFD feed, the distributor will become aware of the irregularity when an original VFD doesn't arrive within 5 days. Such a violation is difficult to hide.

One comment asked who is held responsible, the veterinarian, feeder (client), or feed distributor, if the actual VFD is not properly distributed. While all bear responsibility, the veterinarian is most in control. Thus, we believe it is the veterinarian's obligation to assure that the original VFD is distributed to the feed distributor with the timeliness required by § 558.6(b)(4). The client has responsibility for notifying the veterinarian where to send the original VFD. We recognize there may be instances where a VFD may not be presented to a distributor for several days, and there may be instances where the VFD is issued but never used. If it is determined that a VFD may be refilled, it is possible that the VFD may be required by one distributor first and later by another for refill. In these situations, the client must keep the issuing veterinarian advised when a VFD is moved from one distributor to another, to ensure that the original VFD is moved to the new distributor or a new VFD is issued.

Regarding telephone orders, one comment stated that there is precedence for telephone orders in that veterinarians currently telephone in prescription drug orders. The orders are reduced to writing by the pharmacist without a followup hard copy of the prescription being sent. We do not agree that the situations are the same. The pharmacist who fills a prescription has

extensive training in drug use and potential misuse. Further, a limited amount of information is required in a typical prescription order. Conversely, an extensive amount of information is required in a VFD. A feed mill employee, while skilled in manufacturing feed, may not have the necessary skills to routinely assure a complete and accurate transmission of a VFD or to recognize a potentially inaccurate VFD order. We believe that allowing a telephone order to the feed mill would jeopardize the integrity of the VFD process. Therefore, we have not included telephone orders as an option for transmitting a VFD and have added § 558.6(b)(5) to state that a VFD may not be transmitted by phone.

B. Refills and Length of Time VFD is Valid

(Comment 2) One comment suggested that FDA determine whether refills or reorders are appropriate. Another comment suggested that the veterinarian should be allowed to determine when refills or reorders are necessary. Two comments stated that a single VFD could cover multiple production groups when a disease outbreak is anticipated in subsequent groups of animals passing through a production facility. Concerning the length of time a VFD is valid, two comments stated that the VFD should be valid for up to 6 months. Two other comments stated the opinion that the duration of a VFD should be determined on a case-by-case basis as part of the VFD drug approval process.

We believe that there are situations when refills and expiration dates, possibly of several months, are appropriate to medicate multiple production groups and provide efficient treatment of sick animals. We further believe that allowances of this type will vary considerably depending on the drug and its use. Since we cannot predict what types of drugs and disease situations will be presented in the future, the issues of refills and reorders and the duration of time a VFD can be valid need to be considered on a drug-by-drug basis as part of the new animal drug approval process. We recognize this could result in different conditions for different VFD drugs, which is additional support for the role of the professional (veterinarian) and the need for a complete VFD. Therefore, we have not attempted to specify the allowable number of refills or reorders, or the duration of time a VFD can be valid. This will be dealt with when the new animal drug application (NADA) for the VFD drug is reviewed during the approval process.

C. Classification of VFD Drugs as Category II Drugs

(Comment 3) Two comments asked that we reexamine our decision to automatically classify VFD drugs as Category II drugs. We continue to believe that classifying VFD drugs as Category II drugs is appropriate. Classifying a drug as Category II adds additional regulatory controls because feed manufacturing facilities must possess a medicated feed mill license and be registered with FDA in order to manufacture a Type B or Type C medicated feed from a Category II, Type A medicated article. Registered feed mills are required to be inspected at least every 2 years. Such inspections will help the agency ensure that VFD requirements are met.

Therefore, our decision to automatically classify VFD drugs as Category II drugs remains and is so reflected in the final rule.

D. Responses to Remaining Comments

(Comment 4) Two comments suggested that the “notification letter” of proposed § 558.6(d)(1) and the “acknowledgment letter” of § 558.6(d)(2) be combined into a single letter to reduce the paperwork burden. We are unable to agree to this because these letters serve different purposes and are sent to different entities. The notification letter is sent by the distributor to FDA to notify the agency that the distributor has begun distributing VFD feeds. In contrast, the acknowledgment letter is sent to the distributor by a purchaser stating that it will sell the VFD feed only to a producer with a valid VFD, or to another distributor who provides a similar acknowledgment letter.

We are, however, combining § 558.6(d)(2)(i) and (d)(2)(ii) of the proposed rule, which required in paragraph (d)(2)(i) that a distributor obtain an acknowledgment letter and in paragraph (d)(2)(ii) that a distributor obtain a statement affirming that a consignee-distributor has complied with “distributor notification” requirements. Both requirements may now be met in a single letter under § 558.6(d)(2).

(Comment 5) Two comments asked for other changes in the VFD. One comment asked that § 558.6(a)(3) be changed to read: “You must complete all of the information required on the VFD in writing, and sign it; VFD’s that contain incomplete information will be considered invalid.” A similar comment asked that we consider as unacceptable a VFD that is not filled out completely. We agree with these suggestions and

have incorporated them into § 558.6(a)(3) and (a)(4) in the final rule.

(Comment 6) Two comments asked that the VFD drug sponsor provide VFD forms in triplicate to the veterinarian and that the veterinarian be required to use them. We agree with this comment in part. We addressed it in the proposed rule by revising the new animal drug regulations at § 514.1(b)(9) (21 CFR 514.1(b)(9)) to require the sponsor of a VFD drug to include in the NADA a format for a VFD form as described in § 558.6(a)(4) of this regulation. One comment additionally suggested that using the VFD drug sponsor’s VFD form would eliminate the problem of partially completed forms generated by a veterinarian. While we have not made it mandatory that the VFD drug sponsor provide copies of this form for use by the veterinary profession, we believe that they will make the forms available in triplicate for the sake of efficiency and completeness of the veterinarian’s VFD transmissions. Nevertheless, we continue to give the veterinarian the option of creating his/her own VFD.

(Comment 7) One comment asked that we clarify what we mean by the term “immediately” in § 558.6(b)(4), relating to length of time a veterinarian has to provide the signed original VFD to the distributor as followup to a facsimile or electronic transmission. One comment suggested that we use the term “promptly.” Another comment suggested that the time be 24 hours. We have revised the regulation to read, “the distributor receives the original signed VFD within 5 working days of receipt of the facsimile or other electronic order.” We feel this is sufficient time for the client to place the order and the distributor to receive the signed original mailed by the veterinarian.

Additionally, a comment suggested that the client should not be required to wait to receive the VFD medicated feed until the distributor receives the original VFD. We agree, but to alleviate concern that a client may receive medicated feed containing a VFD drug without receiving a copy of the VFD, we have added § 558.6(c)(4) that reads: “All involved parties must have a copy of the VFD before distribution of a VFD feed to the ultimate user.” The copy need not be an original and may be transmitted by facsimile or other electronic means.

(Comment 8) One comment recommended that the facsimile of the VFD order be on company letterhead. We anticipate that when veterinarians do not use the VFD drug sponsor’s VFD, they will be issuing the VFD on their or their own firm’s stationary. However, even if they do not use letterhead paper, the veterinarian is required to include

his/her name (and signature), address, and license number on the VFD. Therefore, we do not think it is necessary to require them to use company stationary.

(Comment 9) One comment objected to our inclusion of VFD drugs in § 510.300(a)(4) (21 CFR 510.300(a)(4)) because doing so would essentially confer prescription drug status on VFD drugs for submission of promotional materials. Proposed modifications to § 510.300 do not make a VFD drug a prescription drug. Section 504(c) of the act (21 U.S.C. 354(c)) states that VFD drugs cannot be prescription articles. Section 504(b) of the act establishes misbranding criteria for both labeling and advertising for VFD's. Thus, routine requirements for submitting advertising for VFD drug experience reports under § 510.300(a)(4) should be the same as requirements for submitting labeling. We have not changed the proposed provision in the final rule.

(Comment 10) One comment suggested that FDA consider a provision to revoke a veterinarian's right to order use of VFD drugs if the veterinarian fails to have a valid veterinarian-client-patient relationship (VCPR) or fails to provide complete VFD information to the feed distributor. Normally, this type of action would be handled by State veterinary license authorities. However, the act does provide FDA with other regulatory options.

Section 504 of the act states “* * * When labeled, distributed, held, and used in accordance with this section, a veterinary feed directive drug and any animal feed bearing or containing a veterinary feed directive drug shall be exempt from section 502(f) [of the act].” Under section 502(f) of the act (21 U.S.C. 352(f)) a drug or device is misbranded unless its labeling bears adequate directions for lay use. (See 21 CFR 201.5.)

VFD drugs and animal feed bearing or containing veterinary feed directive drugs are exempt from the statutory requirements for adequate directions for lay use only when they are distributed under a VFD issued by a licensed veterinarian within the confines of a valid VCPR and contain complete and accurate information as required by § 558.6.

If the order for a VFD drug is not based upon a valid VCPR or fails to provide complete information as required by § 558.6, then the VFD drug is subject to section 502(f) of the act. Since a VFD drug, by its very nature, cannot bear adequate directions for lay use, a VFD drug subject to 502(f) of the act is misbranded and the veterinarian who issued the VFD may be held

responsible for causing the misbranding of the VFD drug or the feed containing the VFD drug in violation of the act.

We have made nonsubstantive wording and restructuring changes to §§ 514.1(b)(9), 558.3(b)(6), and 558.6(a)(2), (c)(1), (c)(2), and (c)(3) for the sake of clarity.

III. Conforming Changes

FDA has made conforming changes to §§ 514.1(b)(9) and 510.300, and is removing § 558.618(d)(4).

IV. Environmental Impact

We have carefully considered the potential environmental effects of this final rule and have determined that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

V. Federalism

We have analyzed this final rule in accordance with the principles set forth in Executive Order 13132. We have determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, we conclude that the rule does not contain policies that have federalism implications as defined in the order and, consequently, a federalism summary impact statement is not required.

VI. Analysis of Impacts

We have examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612) (as amended by subtitle D of the Small Business Regulatory Fairness Act of 1996 (Public Law 104–121)), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). We believe that this final rule is consistent with the regulatory philosophy and principles identified in the Executive order. In addition, the final rule is not a significant regulatory action as defined by the Executive order and so is not

subject to review under the Executive order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities unless the rule is not expected to have a significant impact on a substantial number of small entities. As this final rule will not impose significant new costs on any firms under the Regulatory Flexibility Act (5 U.S.C. 605(b)), we certify that the final rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

VII. Unfunded Mandates Reform Act of 1995

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare an assessment of the anticipated costs and benefits before requiring any expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million or more (adjusted annually for inflation).

The Unfunded Mandates Reform Act of 1995 does not require FDA to prepare a statement of costs and benefits for the final rule, because the rule is not expected to result in any 1-year expenditure that would exceed \$100 million adjusted for inflation. The current inflation-adjusted statutory threshold is \$110 million.

VIII. Paperwork Reduction Act of 1995

This final rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). A description of these provisions is given below. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

Title: Animal Drug Availability Act; Veterinary Feed Directive

Description: FDA is publishing this final rule to implement provisions of the ADAA which, by adding section 504 to the act, created a new class of animal drugs called VFD drugs. This final rule establishes regulatory requirements for the distribution and use of VFD drugs. VFD drugs are new animal drugs intended for use in or on animal feed whereby such use is permitted only under the professional supervision of a licensed veterinarian operating within the confines of a valid VCPR.

The VFD ordered by the veterinarian must be issued in accordance with the format described under § 558.6(a). We are amending the new animal drug regulations at § 514.1(b)(9) to require the VFD drug sponsor to submit such format as part of the NADA. The format may be used by the sponsor to produce forms in triplicate for use by the veterinarian or it may be supplied to the veterinarian for use in preparing a practice-specific form. Veterinarians are required to complete the VFD in triplicate, authorizing a client-recipient to obtain and use a medicated feed containing a VFD drug. The original copy of the VFD must be forwarded either by the veterinarian or the client-recipient to the distributor providing the VFD. In addition, the veterinarian issuing the VFD and the client-recipient of the VFD must retain a copy of each VFD for 2 years from date of issuance. Any person who distributes medicated feed containing VFD drugs must file with us

a one time notification letter of intent to distribute, and retain a copy of each VFD serviced or each consignee's acknowledgment letter for 2 years. Distributors are also required to keep records of receipt and distribution of medicated animal feeds containing VFD drugs for 2 years. An acknowledgment letter must be provided to a distributor by a consignee who is not the ultimate user of the medicated feed containing a VFD drug. The acknowledgment letter affirms that the consignee will not ship such medicated animal feed to an animal production facility that does not have a VFD, and will not ship such feed to another distributor without receiving a similar acknowledgment letter. To maintain an accurate data base for distributors of VFD drugs, a distributor is required to notify us of any change in name or business address.

In response to a comment, we combined § 558.6(d)(2)(i) and (d)(2)(ii) of the proposed rule, which required in

paragraph (d)(2)(i) that a distributor obtain an acknowledgment letter and in paragraph (d)(2)(ii) that a distributor obtain a statement affirming that a consignee-distributor has complied with "distributor notification" requirements. Both requirements may now be met in a single letter under § 558.6(d)(2). This change does not entail a substantive modification to the reporting burden, so the estimates in table 1 of this document have not changed.

Description of Respondents: Veterinarians, distributors of animal feeds containing VFD drugs, and clients using medicated feeds containing VFD drugs. In the **Federal Register** of July 2, 1999 (64 FR 35966), FDA requested comments on the proposed collection of information. No comments were received on the estimated annual burdens. The annual burden estimates therefore remain unchanged.

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN¹

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
558.6(a)(3) through (a)(5)	15,000	25	375,000	0.25	93,750
558.6(d)(1)(i) through (d)(1)(iii)	5,000	1	5,000	0.25	1,250
558.6(d)(1)(iv)	100	1	100	0.25	25
558.6(d)(2)	5,000	1	5,000	0.25	1,250
514.1(b)(9)	1	1	1	3	3
Total Hours					96,278

¹There are no capital costs or operating and maintenance costs associated with this collection of information.

TABLE 2.—ESTIMATED ANNUAL RECORDKEEPING BURDEN¹

21 CFR Section	No. of Recordkeepers	Annual Frequency per Recordkeeping	Total Annual Records	Hours per Record	Total Hours
558.6(c)(1) and (d)(2)	112,500	10	1,125,000	0.0167	18,788
558.6(e)(ii)	5,000	75	375,000	0.0167	6,263
Total Hours					25,051

¹There are no capital costs or operating and maintenance costs associated with this collection of information.

Individuals and organizations may submit comments on this burden estimate or on any other aspect of these information collection provisions, including suggestions for reducing the burden, and should direct them to George Graber, Center for Veterinary Medicine (HFV-220), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855. The information collection provisions in this final rule have been approved under OMB control number 0910-0363. This approval expires October 31, 2002. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it

displays a currently valid OMB control number.

List of Subjects

21 CFR Part 510

Administrative practice and procedure, Animal drugs, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 514

Administrative practice and procedure, Animal drugs, Confidential business information, Reporting and recordkeeping requirements.

21 CFR Part 558

Animal drugs, Animal feeds.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 510, 514, and 558 are amended to read as follows:

PART 510—NEW ANIMAL DRUGS

1. The authority citation for part 510 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 360b, 371, 379e.

§ 510.300 [Amended]

2. Section 510.300 *Records and reports concerning experience with new animal drugs for which an approved application is in effect* is amended in

paragraph (a)(4) by adding the phrase “or a veterinary feed directive drug” following “if it is a prescription new animal drug”.

PART 514—NEW ANIMAL DRUG APPLICATIONS

3. The authority citation for part 514 continues to read as follows:

Authority: 21 U.S.C. 351, 352, 360b, 371, 379e, 381.

4. Section 514.1 is amended by adding paragraph (b)(9) to read as follows:

§ 514.1 Applications.
* * * * *

(b) * * *
(9) *Veterinary feed directive.* Three copies of a veterinary feed directive (VFD) must be submitted in the format described under § 558.6(a)(4) of this chapter.

* * * * *

PART 558—NEW ANIMAL DRUGS FOR USE IN ANIMAL FEEDS

5. The authority citation for 21 CFR part 558 continues to read as follows:

Authority: 21 U.S.C. 360b, 371.

6. Section 558.3 is amended by revising paragraph (b)(1)(ii) and by adding paragraphs (b)(6) through (b)(11) to read as follows:

§ 558.3 Definitions.
* * * * *

(b) * * *
(1) * * *
(ii) Category II—These drugs require a withdrawal period at the lowest use level for at least one species for which they are approved, or are regulated on a “no-residue” basis or with a zero tolerance because of a carcinogenic concern regardless of whether a withdrawal period is required, or are a veterinary feed directive drug.

* * * * *

(6) A “veterinary feed directive (VFD) drug” is a new animal drug approved under section 512(b) of the Federal Food, Drug, and Cosmetic Act (the act) for use in or on animal feed. Use of a VFD drug must be under the professional supervision of a licensed veterinarian.

(7) A “veterinary feed directive” is a written statement issued by a licensed veterinarian in the course of the veterinarian’s professional practice that orders the use of a veterinary feed directive (VFD) drug in or on an animal feed. This written statement authorizes the client (the owner of the animal or animals or other caretaker) to obtain and use the VFD drug in or on an animal

feed to treat the client’s animals only in accordance with the directions for use approved by the Food and Drug Administration (FDA). A veterinarian may issue a VFD only if a valid veterinarian-client-patient relationship exists, as defined in § 530.3(i) of this chapter.

(8) A “medicated feed” means a Type B medicated feed as defined in paragraph (b)(3) of this section or a Type C medicated feed as defined in paragraph (b)(4) of this section.

(9) For the purposes of this part, a “distributor” means any person who distributes a medicated feed containing a VFD drug to another distributor or to the client-recipient of the VFD.

(10) An “animal production facility” is a location where animals are raised for any purpose, but does not include the specific location where medicated feed is made.

(11) An “acknowledgment letter” is a written communication provided to a distributor by a consignee who is not the ultimate user of medicated feed containing a VFD drug. An acknowledgment letter affirms that the consignee will not ship such medicated animal feed to an animal production facility that does not have a VFD, and will not ship such feed to another distributor without receiving a similar written acknowledgment letter.

7. Section 558.6 is added to subpart A to read as follows:

§ 558.6 Veterinary feed directive drugs.

(a) What conditions must I meet if I am a veterinarian issuing a veterinary feed directive (VFD)?

- (1) You must be appropriately licensed.
- (2) You must issue a VFD only within the confines of a valid veterinarian-client-patient relationship (see definition at § 530.3(i) of this chapter).
- (3) You must complete the VFD in writing and sign it or it will be invalid.
- (4) You must include all of the following information in the VFD or it will be invalid:
 - (i) You and your client’s name, address and telephone and, if the VFD is faxed, facsimile number.
 - (ii) Identification and number of animals to be treated/medicated feed, including identification of the species of animals, and the location of the animals.
 - (iii) Date of treatment, and, if different, date of prescribing the VFD drug.
 - (iv) Approved indications for use.
 - (v) Name of the animal drug.
 - (vi) Level of animal drug in the feed, and the amount of feed required to treat the animals in paragraph (a)(4)(ii) of this section.

(vii) Feeding instructions with the withdrawal time.

(viii) Any special instructions and cautionary statements necessary for use of the drug in conformance with the approval.

(ix) Expiration date of the VFD.

(x) Number of refills (reorders) if necessary and permitted by the approval.

(xi) Your license number and the name of the State issuing the license.

(xii) The statement: “Extra-label use, (i.e., use of this VFD feed in a manner other than as provided for in the VFD drug approval) is strictly prohibited.”

(xiii) Any other information required by the VFD drug approval regulation.

(5) You must produce the VFD in triplicate.

(6) You must issue a VFD only for the approved conditions and indications for use of the VFD drug.

(b) What must I do with the VFD if I am a veterinarian?

(1) You must give the original VFD to the feed distributor (directly or through the client).

(2) You must keep one copy of the VFD.

(3) You must give the client a copy of the VFD.

(4) You may send a VFD to the client or distributor by facsimile or other electronic means provided you assure that the distributor receives the original signed VFD within 5 working days of receipt of the facsimile or other electronic order.

(5) You may not transmit a VFD by telephone.

(c) What are the VFD recordkeeping requirements?

(1) The VFD feed distributor must keep the VFD original for 2 years from the date of issuance. The veterinarian and the client must keep their copies for the same period of time.

(2) All involved parties must make the VFD available for inspection and copying by FDA.

(3) All involved parties (the VFD feed distributor, the veterinarian, and the client) must keep VFD’s transmitted by facsimile or other electronic means for a period of 2 years from date of issuance.

(4) All involved parties must have a copy of the VFD before distribution of a VFD feed to the ultimate user.

(d) What are the notification requirements if I am a distributor of animal feed containing a VFD drug?

(1) You must notify FDA only once, by letter, that you intend to distribute animal feed containing a VFD drug.

(i) The notification letter must include the complete name and address of each business site from which distribution will occur.

(ii) A responsible person from your firm must sign and date the notification letter.

(iii) You must submit the notification letter to the Center for Veterinary Medicine, Division of Animal Feeds (HFV-220), 7500 Standish Pl., Rockville, MD 20855, prior to beginning your first distribution.

(iv) You must notify the Center for Veterinary Medicine at the above address within 30 days of any change in name or business address.

(2) If you are a distributor who ships an animal feed containing a VFD drug to another consignee-distributor in the absence of a valid VFD, you must obtain an "acknowledgment letter," as defined in § 558.3(b)(11), from the consignee-distributor. The letter must include a statement affirming that the consignee-distributor has complied with "distributor notification" requirements of paragraph (d)(1) of this section.

(e) What are the additional recordkeeping requirements if I am a distributor?

(1) You must keep records of receipt and distribution of all medicated animal feed containing a VFD drug.

(2) You must keep these records for 2 years from date of receipt and distribution.

(3) You must make records available for inspection and copying by FDA.

(f) What cautionary statements are required for VFD drugs and animal feeds containing VFD drugs? All labeling and advertising must prominently and conspicuously display the following cautionary statement: "Caution: Federal law limits this drug to use under the professional supervision of a licensed veterinarian. Animal feed bearing or containing this veterinary feed directive drug shall be fed to animals only by or upon a lawful veterinary feed directive issued by a licensed veterinarian in the course of the veterinarian's professional practice."

§ 558.618 [Amended]

8. Section 558.618 *Tilmicosin* is amended by removing paragraph (d)(4).

Dated: November 30, 2000.

Margaret M. Dotzel,

Associate Commissioner for Policy.

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