72

Guidance For Industry

GMP'S FOR MEDICATED FEED MANUFACTURERS NOT REQUIRED TO REGISTER AND BE LICENSED WITH FDA

This document is intended to help manufacturers of medicated feed, that are not required to register and be licensed with the FDA, comply with the Current Good Manufacturing Practice regulations, 21 CFR 225.120-225.202.

This guide represents the agency's current thinking on compliance with these regulations. It does not create or confer any rights for or on any person and does not operate to bind the FDA or public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations or both.

Comments and suggestions regarding the document should be submitted to George Graber, Center for Veterinary Medicine, (HFV-220), Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, 301-827-6651, E-mail: ggraber@bangate.fda.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center For Veterinary Medicine
May 1998

GMPs FOR MEDICATED FEED MANUFACTURERS NOT REQUIRED TO REGISTER AND BE LICENSED WITH FDA

FOREWORD

A most important responsibility of an animal feed manufacturer is to assure that the feed produced--whether medicated or non-medicated--meets the intended specifications and is not adulterated. All feed mixing operations, regardless of size or drugs used, share this responsibility. Medicated feeds must be proper with respect to drug content to have their intended effect. Medicated and non-medicated feeds that are adulterated with undesired drugs may cause violative drug residues in meat, milk or eggs, or injury to consuming animals. Everyone associated with food animal agriculture must work to avoid these risks to the public and animal health, and the potential loss of consumer confidence in animal-derived food products.

The Food and Drug Administration (FDA) established the Current Good Manufacturing Practice (CGMP) Regulations for Medicated Feeds through public rulemaking. The CGMPs provide guidance for medicated feed manufacturers to assure that their products meet the identity, strength and quality which they should possess with respect to their drug content. The regulations apply equally to all manufacturers of medicated feeds using the same drug sources. The regulations are divided into two sections. The first section applies to facilities utilizing drug sources which require licensing and registration with FDA. This section is more comprehensive and detailed than the second section. The second section applies to those facilities which are not required to be licensed and registered. Medicated feeds must be manufactured in accordance with the appropriate applicable section of the CGMP Regulations to comply with the law.

This guide is designed to provide information and answer typical questions about the regulatory responsibilities of the manufacturers of medicated feeds who are not licensed and registered with FDA and, hence, are subject to the requirements of the less detailed CGMP Regulations.

BASIC INFORMATION

Q. Who must comply with "Current Good Manufacturing Practices?"

A. All manufacturers of medicated feed must follow CGMPs. Anyone producing an animal feed containing an animal drug is subject to this requirement. This includes large multi-plant manufacturers and single-plant manufacturers, as well as on-farm mixing operations.

Q. What is the legal basis for requiring compliance with CGMPs?

A. The Federal Food, Drug, and Cosmetic Act (the Act) Section 501 (a)(2)(B) states that a medicated feed containing an animal drug is adulterated if not produced in conformance with CGMPs. Adulterated feeds and manufacturers of adulterated feed are subject to regulatory action.

Q. Does the term "medicated feed" mean only a complete feed, one that can be fed as the sole ration?

A. The term "medicated feed" includes all medicated feed products intended to be a substantial source of nutrients in the diet of an animal. It includes products commonly referred to as supplements, concentrates, premix feeds, and base mixes. It is not limited to complete feeds intended to be the sole ration of the animal.

Q. Where are the CGMPs described?

A. Regulations describing CGMPs have been published by FDA in the *Code of Federal Regulations* (CFR), Part 225. There are two sections of these regulations--one for mills registered with FDA to use drug sources requiring approved medicated feed mill licenses, and one for mills using only drug sources which do not require such licenses and registration with FDA. This booklet addresses the non-registered, non-licensed mill CGMP regulations.

Q. How does following the CGMPs benefit me as a manufacturer of medicated feed?

A. Observance of CGMPs should result in medicated animal feeds that meet product specifications. This will help assure that meat, milk, and eggs produced with these feeds contain no violative drug residues. Non-compliance with the CGMPs carries the potential of medicated feed products which could cause harm to consuming animals or result in unsafe drug residues in the edible products from these animals.

CGMP REGULATIONS AND COMMENTS

The text of the CGMP regulations for non-registered, non-licensed mills, as printed in the CFR, is reproduced below. Each paragraph is followed with pertinent comments to aid in understanding the requirements and how to meet them.

CURRENT GOOD MANUFACTURING PRACTICE FOR MEDICATED FEEDS

Subpart F -- Facilities and Equipment

o 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.

Comment: Buildings and grounds should be suitable for their use and facilitate the production of feeds that are proper in all respects. Construction, maintenance, and upkeep should provide protection from the elements and pests. The key elements are **suitability and good housekeeping**.

o 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).

Comment: Equipment must be suitable for its purpose. It must be of proper size and design for the function performed to have the inherent needed capability to produce good products. Good maintenance is equally important. The key elements are **accuracy, capability, and good maintenance**.

o 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 feeds.

Comment: Contamination of feed with potentially toxic non-feed substances is to be avoided. Keep all potential contaminants out of feed production areas to preclude accidental contamination of feed. The key element is to **prevent contamination**.

Subpart G -- Product Quality Assurance

o 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.

Comment: It is vital that the identity and quality of drug sources be maintained, and that the labeled instructions for their use are followed. The key elements are **continuous drug identification and protection, written inventory control, and adherence to label instructions**.

o 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, investigations and corrective action shall be implemented immediately by the firm and such records shall be maintained on the premises for a period of 1 year.

Comment: Any indication of a breakdown in controls or that a mistake may have occurred requires a quick check to determine if there is a problem. This must be followed with any needed corrective action. A written record of the investigation, conclusions, and actions taken is to be made and retained. The key elements are to **react, correct, and record**.

o 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 non-medicated feeds.

Comment: Production and control procedures should be established to prevent unsafe contamination of feeds by residual medicated feed material in production and distribution systems. The key element is **prevent unsafe carryover**.

Subpart H -- Labeling

o 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.

Comment: Controls over labels shall ensure that labels are correct and that the proper label is used on all feeds. Labels must identify the product, drug content and purpose, and how the medicated feed is to be used. The key element is **correct labels on all feeds.**

Subpart I -- Records

o 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 1 year following the date of last distribution.

Comment: Records and procedures, including labeling, must provide a meaningful history of product production and distribution. This will enable a specific product to be located and returned if this is necessary. The key elements are **complete written records and recall capability.**

OPERATIVE TERMS

Q. What drug products used in medicated feeds are covered by CGMPs?

A. All animal feeds containing animal drugs (medications) are covered by CGMPs.

Q. Are all animal feed drugs regulated the same with respect to CGMPs?

A. No. The applicable CGMP Requirements are based on the categorization of the drug and the potency. All drugs are placed into one of two categories based on whether or not there is a withdrawal requirement at the lowest continuous feeding level and the potential for harmful effect from misuse of the drug.

Q. What are the two categories of drugs?

A. The two categories of drugs are known as "Category I" and "Category II."

Category I consists of those drugs for which no withdrawal period is required at the lowest continuous feeding level for any approved species. Category I drugs do not require an approved Medicated Feed Mill License for manufacturing of medicated feeds unless they are combined with a Category II drug source requiring a Medicated Feed Mill License.

Category II consists of drugs that either require a withdrawal period at the lowest feeding level in at least one species for which the drug is approved, or are regulated on a "no-residue" basis because of a carcinogenic concern. Higher potency sources (Type A products) of Category II drugs require a Medicated Feed Mill License to manufacture medicated feeds. Lower potency sources (Type B products) are subject to the same requirements as Category I drugs.

Q. What are the medicated product types?

A. There are three (3) medicated product types: Type A, Type B, and Type C. These terms replace "medicated premix, concentrate, supplement, and complete feed," which are no longer being used in FDA's regulations. The Type A product is considered a drug, and the Type B and C products are medicated feeds. A Type A medicated article is a product that consists of one or more new animal drugs intended for use in the manufacture of a medicated feed. It is the subject of an approved new animal drug application. A Type B medicated feed is intended solely for the manufacture of other medicated feeds (Type B or Type C). A Type C medicated feed is a complete feed for the animal, or is a feed that may be fed "top-dressed" or offered "free-choice" in conjunction with other animal feed.

REGISTRATION

Q. What feed manufacturing establishments must register with FDA?

A. Any feed manufacturing establishment that uses one or more Type A sources of Category II drugs to manufacture medicated feeds must register with FDA as a medicated feed establishment. Registration is not required if drug use is limited to Category I drugs (all types) and Type B sources of Category II drugs--that is, no Medicated Feed Mill License is held.

Q. Where can I find information on the procedures for registration if I desire to register and obtain a Medicated Feed Mill License?

A. Procedures for registration can be obtained from a local FDA office or you can write to the Drug Listing Branch (HFD-334), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, Maryland 20857.

Q. What about producers who mix their own feed?

A. All manufacturers of medicated feeds are subject to the same rules. If firms (commercial mills, feedlots, producers, mobile mixers, etc.) use only Category I products and/or Category II Type B drug products, registration with FDA is not required. These manufacturers must comply with the medicated feed CGMPs in 21 CFR Parts 225.120 to 225.202 (the less detailed set of CGMPs). They are not subject to biennial inspection by FDA.

If a firm uses one or more Category II Type A medicated articles as drug sources, it must register with FDA and comply with the medicated feed CGMPs in 21 CFR Parts 225.10 to 225.115 (the more detailed set of CGMPs). As a registered establishment, it is subject to inspection by FDA or FDA-commissioned State inspectors at least once every two years for compliance with these CGMPs.

INSPECTIONS

Q. When are feed manufacturers inspected?

A. All registered feed manufacturers are subject to at least one inspection during each two-year period. This inspection requirement is waived for those manufacturers not required to register.

Q. Will my feed manufacturing operation be inspected if it is not required to be registered?

A. There will be no routine FDA biennial inspection. The fact that a feed manufacturing operation is not registered, however, does not mean that it is totally exempt from Federal inspection. An FDA investigator or an FDA-commissioned State inspector may conduct an inspection to confirm registration status of the firm or to follow up on a report of a drug residue, or for other appropriate reasons. Also, your State feed control office may conduct routine inspections to determine compliance of your facility with the less detailed CGMPs.

Q. How can I, as a non-registered feed manufacturer, avoid problems?

A. By knowing the CGMP regulations and by self-inspecting your own establishment, you can determine if your operation complies with the spirit and intent of the regulations. Non-compliance may result in product adulteration and unacceptable risks to animal and/or public health. Ensure that all employees involved in the manufacture of medicated feeds have an understanding of the manufacturing and control operation(s) which they perform, including the location and proper use of equipment, and that all necessary procedures and controls are in place and followed.

Q. What should I look for when I inspect my own feed manufacturing operation?

A. Self-inspections of non-registered feed manufacturers should cover at least the following areas:

A. Facilities and Equipment

- *225.120 Buildings and grounds*: Is there adequate space for equipment, and processing and storage of medicated feeds? Does construction and maintenance minimize vermin and pest infestation?

- *225.130 Equipment*: Is equipment capable of producing a medicated feed of intended potency and integrity? Are adequate cleanout procedures used to avoid unsafe contamination of medicated and non-medicated feeds? Such procedures may include physical cleanout, flushing, sequencing of production, and similar actions. Are scales and metering devices accurate and suitable for their intended purposes?

- *225.135 Work and Storage Areas*: Are work areas, drug storage, and equipment free of pesticides, fertilizers and other toxic substances that could contaminate feeds?

B. Product Quality Assurance

- *225.142 Components*: Have adequate procedures been established and maintained for the identification, storage and inventory control of all drug sources intended for use in the manufacturing of medicated feeds? Are the procedures and records adequate to permit detection of incorrect use?

- *225.158 Laboratory Assays*: Have necessary corrective actions been determined and taken when laboratory assays of drug components indicated a medicated feed was not within permissible limits? Are these records kept for at least one year?

- *225.165 Equipment Cleanout Procedures*: Have adequate procedures been established to prevent unsafe contamination of feeds? Are they followed?

C. Labeling

- *225.180 Labeling*: Are labels received, handled and stored in a manner that ensures correct labeling and prevents mix-ups? Are all medicated feeds adequately labeled?

D. Records

- *225.202 Records*: Are written records kept containing the formula, date of mixing, and date of shipment (if not for own use)? Can you locate and recall product if this is necessary?

ENFORCEMENT

Q. What will happen if my operation fails a CGMP inspection?

A. The objective of FDA regulatory programs is to encourage and assure medicated feeds are properly manufactured and labeled. Enforcement activities include actions to correct and prevent violations, remove violative products or goods from the market, and punish offenders. Enforcement efforts range from a letter notifying the individual or firm of a violation and requesting correction, to seizure of product, to criminal prosecution of the individual or firm. The type of action recommended for failure to follow CGMPs will depend upon the nature of the violation and the public health concern, FDA policy, previous history of violations by the firm, and other factors. Your State may have a similar range of enforcement efforts under its authority.

OTHER INFORMATION

Q. Does the FDA have other information available for use by the medicated feed manufacturer?

A. Yes. The following documents offer additional information about FDA and your responsibility as a feed manufacturer. These materials are free and available upon request from the Center for Veterinary Medicine, Communications Staff, HFV-12, 7500 Standish Place, Rockville, Maryland 20855. Some of these materials are available on CVM's Internet Web Site at **http://www.fda.gov/cvm**.

1. FDA Compliance Program 7371.004 -- Medicated Feeds (FY 94 - 98)

2. *Code of Federal Regulations*, Part 225, Current Good Manufacturing Practice Regulations for Medicated Feeds

3. *Code of Federal Regulations*, Part 558, New Animal Drugs for Use in Animal Feeds

4. Guidance Document #68 -- Small Entities Compliance Guide for Protein Blenders, Feed Manufacturers, and Distributors