SUBJECT:	IMPLEMENTATION DATE:
Feed Manufacturing	**UPON RECEIPT**
	COMPLETION DATE: **Continuing**

DATA REPORTING

PRODUCT CODES	PRODUCT/ASSIGNMENT CODES
INDUSTRY CODES: 69	**71004** (CGMP) **71004A** (NON-CGMP) **71S004** (State Contract)

1. **Hard Copy Reporting**

When a District becomes aware of any significant adverse information that affects the Agency's licensing decisions on a firm, the District should immediately notify the Center for Veterinary Medicine (CVM) Division of Compliance contact (HFV-230) by e-mail (paul.bachman@fda.hhs.gov) or FAX (240-276-9241), HFV-230, in turn, will convey the information to other interested CVM units.

Send copies of the Establishment Inspection Report (EIR) sheets for those Out-of-Business (OOB) or Not Official Establishment Inventory (NOEI) firms to HFV-226. Also send a copy of the cover sheet(s) to HFD-095 for cancellation of Drug Registration.

Forward Attachment B to HFV-226 if a firm is withdrawing its license. Forward copies of all Warning Letters to HFV-235, Compliance Information Management Team.

2. **FACTS/Registration Reporting**

a. Charge time for Current Good Manufacturing Practice (CGMP) medicated feed inspections to PAC 71004, or 71S004 if state official is making the inspection. If the inspection covers both Type A Medicated Articles (CP 7371.005/PAC 71005)

and medicated feed manufacturing, be sure to include both PACs on the coversheet.

b. Charge time for NON-CGMP investigations or inspections to PAC 71004A.

c. Charge time for bovine spongiform encephalopathy (BSE) (CP 7371.009) to the appropriate codes listed within that program.

PART I - BACKGROUND

OVERVIEW

This Compliance Program, prior to 2001, had been limited to medicated feed manufacturing. We revised the title of the program to Feed Manufacturing Compliance Program in 2001 since work under this program was now to cover both non-medicated and medicated feed manufacturing. This change was in response to the growing concern over the safety of feed ingredients (such as meat and bone meal, other prohibited mammalian proteins, etc.) and their public health impact. The program added information on Bovine Spongiform Encephalopathy (BSE) and inspectional guidance that addressed several segments of the animal feed industry including non-medicated feed manufacturers, renderers, protein blenders, licensed and unlicensed feed manufacturers, distributors, retailers, on-farm feed mixers, and ruminant feeders. Subsequently, the BSE/Ruminant Feed Ban Inspections compliance program was issued on 10/21/2003. It provided guidance on the inspection and compliance of firms and facilities subject to the regulation prohibiting the utilization of specified animal proteins in ruminant feeds previously included in this Feed Manufacturing program. As a result, the Feed Manufacturing program has been revised to remove the BSE inspectional guidance and program attributes.

The term “animal feed” is defined in Chapter II, Section 201(w) of the Federal Food, Drug, and Cosmetic Act (FFD&C Act) as an article intended for use for food for animals other than man and which is intended for use as a substantial source of nutrients in the diet of the animal, and is not limited to a mixture intended to be the sole ration of the animal. Feed manufacturing is a vital and active industry in the United States (U.S.), providing food for both food-producing animals, and non-food producing animals including household pets, animals used in sporting and zoo animals. Exercising adequate and appropriate control over the ingredients used in these feeds and the process of their manufacture can have significant impact on the health and well-being of the animal. It may also have significant impact on human health, especially for feeds given to food-producing animals. Animal drugs are incorporated into feeds to produce medicated feeds because feed is the most feasible source of administering animal drugs on a daily basis. Regulations in Title 21 Code of Federal Regulations (CFR) Part 558 provide for approved uses of drugs and combinations of drugs in animal feed.

The passage of the Animal Drug Availability Act (ADAA) in October of 1996, abolished medicated feed applications (Form FDA 1900) and established medicated feed mill licenses, (Form FDA 3448). The ADAA amended the FFD&C Act to require a single medicated feed mill facility license to manufacture feeds that were previously covered by multiple Medicated Feed Applications (MFAs). New regulations, contained in 21 CFR Part 515, governing medicated feed mill licenses were published on November 19, 1999.

Any new animal drug approved for use in animal feed is placed in one of two categories, Category I or II (see definitions below). Firms using Category II Type A Medicated Articles to make medicated feeds are required to register with FDA and hold an approved medicated feed mill license. FDA is required to inspect these firms once every two years. Regulations governing the manufacture of medicated feeds are published in 21 CFR Part 225.

The ADAA also created a new category of animal drugs called Veterinary Feed Directive (VFD) drugs. A VFD drug is a new animal drug intended for use in animal feed administered and issued on the written order of and used under the professional supervision of a licensed veterinarian. The regulations for VFD drugs published on December 8, 2000, and are found in 21 CFR 558.6. To date, two VFD drug have been approved, Tilmicosin, 21 CFR 558.618 and florfenicol, 21 CFR 558.261.

On May 28, 2003 (68 FR 31645), in the Federal Register, CVM proposed changes to the regulations for liquid medicated feed and free-choice medicated feed. The purpose of the proposed changes in the regulations for liquid medicated feed was to clarify what data are required to demonstrate chemical and physical stability of a drug in liquid feed, how such data may be submitted for use in the new animal drug approval process, and which liquid medicated feeds may be manufactured in a feed manufacturing facility that has not obtained a medicated feed mill license from FDA. The purpose of the proposed changes in the regulations for free-choice medicated feed was to ensure that they are consistent with the requirements for liquid medicated feed, and that provisions for free-choice medicated feed and liquid medicated feed comply with the terms of the Animal Drug Availability Act (ADAA) of 1996.

The final rule published on May 27, 2004 (69 FR 30194) with an effective date of June 28, 2004. The final rules adopted the proposed rules without change. For both the liquid and free-choice medicated feed final rules, FDA concluded that an approved medicated feed mill license is required for facilities that manufacture feeds using Category II drug(s) or manufacture those products using Category I drug(s) that must follow proprietary formulas or specifications. This means that certain liquid and free-choice medicated feeds will no longer require an approved medicated feed mill license for their manufacture.

DEFINITIONS

Blue Bird Labeling:

Representative Type B and/or Type C medicated feed labeling approved in the Type A Medicated Article New Animal Drug Application (NADA). This template is used by manufacturers as a model to generate actual feed labels.

Carryover:

Cross-contamination of feeds during manufacture with low levels of drugs.

Category I:

Drugs that have no required withdrawal period at the lowest continuous feeding level for any approved animal species.

Category II:

Drugs that either requires a withdrawal period at the lowest continuous feeding use level in at least one animal species for which the drug is approved or are regulated on a "no-residue" basis because of carcinogenic concern.

Commercial Feed Mill:

A feed mill that combines/mixes feed that is distributed or intended to be distributed for use as feed or for mixing in feed for animals.

Custom Formula Mixer:

A mill that mixes commercial feeds or feed ingredients according to the specific instructions of the final customer, which are distributed only to that customer and are not redistributed.

Feedlot:

Refers to feeding cattle in a restricted area with the feed conveyed to the animals. It may involve either an open pen or confinement (sheltered) feeding.

Flushing:

The process of running an ingredient, usually an abrasive-type material such as corn, soybean meal, peanut hulls, etc., through the manufacturing equipment and associated handling equipment (e.g. conveyors) after the production of a batch of feed, for the purpose of cleaning out any drug residue.

Free-choice:

Administration of animal drugs that are approved as and labeled for free-choice feeding, whereby the drugs are mixed into feeds and placed in feeding area; these feeds are not intended to be consumed fully at a single feeding and do not constitute the entire diet of the animal. Examples include lick tanks, blocks and mineral mixes.

Hauler/Distributor:

Persons who distribute or transport feeds or feed ingredients (including animal protein products).

Mixer-Feeder:

This is an operation that mixes feed, which is fed to its own animals or animals under its control. This type of firm is generally a feedlot or an individual farm.

New Animal Drug:

Any drug intended for use for animals other than man, including any drug intended for use in animal feed but not including such feed, the composition of which is not generally recognized as safe and effective by experts.

Type A:

A Type A Medicated Article is a product that consists of one or more new animal drugs intended solely for use in manufacturing another Type A Medicated Article or in the manufacturing of a medicated feed. The medicated feed can be either a Type B Medicated Feed or a Type C Medicated Feed. A Type A Medicated Article is of a standardized potency and is the subject of an approved New Animal Drug Application (NADA) under section 512 of the FFD&C Act.

Type B:

A Type B Medicated Feed is a feed that contains a new animal drug plus a substantial quantity of nutrients (not less than 25% by weight) and is intended solely for use in the manufacturing of another Type B Medicated Feed or a Type C Medicated Feed. A Type B Medicated Feed is produced by diluting a Type A Medicated Article or another Type B Medicated Feed, or is produced from a non-standardized drug component (bulk or "drum-run"), which is a dried crude fermentation product.

If a Type B Medicated Feed is produced from a drug component, it is the subject of an approved NADA under section 512 (c)(1) of the FFD&C Act. If the Type B Medicated Feed is produced from a Category II, Type A Medicated Article, a registered and licensed feed mill must manufacture the feed (21 CFR 558.3 and 21 CFR 207.20).

A Type B Medicated Feed conforms to the definition of animal feed in Section 201 (w) of the FFD&C Act (i.e., intended as a substantial source of nutrients for the animal). Before being fed to animals, it must be substantially diluted with one or more nutrients to produce a Type C Medicated Feed.

The maximum permitted concentration of a drug in a Type B Medicated Feed is 100 times the highest continuous use level for Category II drugs. The "highest continuous use level" is the highest dosage at which a drug is approved for continuous use (14

days or more) or, if not approved for continuous use, the highest level used for disease prevention or control.

The maximum B levels are not cast in concrete; they will change based on approved changes in the new animal drug application. For example, a drug's category could change based on new data, or a higher continuous use level may be approved.

Type C:

A Type C Medicated Feed is a feed that consists of a new animal drug that is intended to be offered as a complete feed for the animal or may be fed top dressed or offered free-choice in conjunction with other animal feed to supplement the animal's total daily ration. A Type C Medicated Feed is produced by substantially diluting a Type A Medicated Article, a Type B or another Type C Medicated Feed or is produced by substantially diluting a drug component with other ingredients to a level of use specified in an approved NADA.

If the Type C Medicated Feed is produced from a Category II, Type A Medicated Article, a registered and licensed feed mill must manufacture the feed. If the Type C Medicated Feed is produced from a drug component, it is the subject of an approved NADA under section 512 of the FFD&C Act.

Veterinary Feed Directive (VFD):

Certain approved new animal drugs will require a VFD to manufacture feed containing that drug (21 CFR 558.6). The VFD is a written order from the veterinarian authorizing the distribution of a specific quantity of medicated feed for a specific producer and animal(s). **THEY ARE NOT PRESCRIPTION** drugs; regulation of animal drugs for use in medicated feeds under traditional prescription systems had proven unworkable in the past since the prescription legend invoked State's pharmacy laws; such application of State pharmacy laws to medicated feeds would have burdened State pharmacy boards and imposed costs on animal feed manufacturers to such an extent that it would have been impractical to make these needed new animal drugs available for animal therapy. Therefore, a new class of restricted feed use drugs that may be distributed without invoking State pharmacy laws was established. It is anticipated the drugs approved for VFD use will be for therapeutic purposes only. Veterinarians must have a valid veterinarian-client-patient relationship to issue these directives and must maintain copies of VFDs issued. Also, there are record retention requirements for Type A manufacturers, manufacturers of feeds covered by a VFD, and producers who feed a VFD feed.

Those who wish to distribute feeds containing VFD drugs (21 CFR 558.6(d)(1)) must notify FDA/CVM of their intent to distribute at the following address:

Center for Veterinary Medicine
HFV-226
7519 Standish Place
Rockville, Maryland 20855

VFD Distributor Notification Letter:

A notification letter is the means by which a facility notifies the Center for Veterinary Medicine of its intent to distribute a VFD product. This is a one time only occurrence.

VFD Acknowledgement Letter:

An acknowledgment letter is provided to a distributor by a purchaser (middleman) stating that it will sell the VFD feed only to a producer with a valid VFD, or to another distributor who provides a similar acknowledgement letter. All acknowledgement letters are subject to inspection and must be kept on file for a minimum of two years.

PART II - IMPLEMENTATION

OBJECTIVES

- To conduct inspections of registered medicated feed firms and determine whether the firms are in compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations.
- To address concerns of drug residue carryover and superpotent and subpotent feeds.
- To verify compliance with VFD requirements as needed.
- To encourage voluntary corrective action by firms when appropriate.
- To initiate administrative and/or regulatory action against violative firms and feed products.

PROGRAM MANAGEMENT INSTRUCTIONS

This program uses inspectional observations to determine whether the feed firm inspected is in compliance with the CGMP requirements listed in 21 CFR Part 225, the Medicated Feed Mill License regulations in 21 CFR Part 515, and the new animal drug regulations in 21 CFR Part 558. Samples are to be collected to document jurisdiction and violations. Samples may be either documentary or physical (see Part III). Samples may also be collected for determination of contamination, and use of inappropriate ingredients.

A. Inspection Priorities

In FY08, CVM began using risk-based criteria for inspection of medicated feed facilities requiring a license. At the beginning of each fiscal year, an assignment will issue from the Center as to which facilities are to be inspected. The list will include the ranking order of each facility within each district. As always, the first priority is for cause inspections. Please schedule in priority order as follows:

1. For Cause (Priority 1)

   Conduct for cause inspections when there is a public health concern or animal deaths, etc.

2. Assignment List (Priority 2)

   Inspect the facilities indicated in the assignment as being the highest priority (tier 1 facilities). As always, re-inspect firms on the list whose most recent inspection was classified Official Action Indicated (OAI) within the allotted time timeframe. Additionally, you should re-inspect an OAI firm within 90 days of issuing the firm a Warning Letter to determine if CGMP violations have been corrected.

3. Pre-Approval Inspections (Priority 3)

   Conduct pre-approval inspections of firms applying for a medicated feed mill license for the first time. The inspection is required to take place before a medicated feed mill license is approved and should take place within 60 days of the filing of a license application. FDA has a 90-day statutory obligation to act on a license application (21 CFR 515.20).

   New applicants may be newly constructed or acquired facilities, or active feed mixers that wish to secure a license. A new facility does not have to be in operation to demonstrate capability and secure a license, but the investigator is to determine the applicant's knowledge of the CGMP requirements and its preparedness to comply.

   When a pre-approval inspection finds a facility not in compliance with the CGMP requirements, the Center should be notified prior to the District recommending a denial of the feed mill license.

B. Inspection Types

1. Surveillance Inspection

   Surveillance inspection is an information gathering operation. There is no reason to believe that there are any problems based on prior history or, in the case of the initial inspection of an establishment, lack of history.

   Conduct surveillance inspections of firms where CVM or the firm has requested pre-approval inspection (Priority 3) and where firms are scheduled for inspection (Priority 4). Surveillance inspections may be converted to compliance inspections when conditions are uncovered that show: (1) that there is a potential for causing unsafe drug residues in food animals, (2) that health problems in animals fed the medicated feed have occurred or may occur, or, (3) where there is a reasonable potential for adversely affecting the quality or other characteristics of the finished feed.

2. Compliance Inspection

A compliance inspection is based on information suggesting that there may be a significant problem or that there actually has been a significant problem that should have been corrected. This information could be the result of sample analyses, prior inspection, recall or other information received by the District. Conduct compliance inspections of those firms with a significant violative history and of those firms involved in a violative tissue residue report (Priority 1).

3. Contract Audit Inspections

For State contract audits refer to FMD 76 for instructions. Use Form FDA 2481 (Medicated Feed Inspection Report, **FDA Form 2481**) to record inspectional observations.

C. Other Drug Related Violations

Be alert for possible sales of prescription animal drugs and determine whether these drugs are sold on the prescription order of a licensed veterinarian. This does not include Veterinary Feed Directive Drugs (VFD). **Note: VFD drugs are not prescription drugs.** Do determine if VFD drugs have been handled correctly. Look for other possible non-CGMP violations, such as the manufacture of medicated feeds without required approvals, illegal combinations, and unapproved sources of drugs, such as soluble powders and bulk drug substances. Be alert for possible storage violations of dosage form animal drugs such as storing injectables without refrigeration when refrigeration is required, etc. Report any activity on Form FDA 2481.

Conduct follow-up inspections of distributors selling Category II Type A Medicated Articles to firms that do not have the required medicated feed mill license.

Contact CVM's Medicated Feeds Team, HFV-226, 240-453-6848, when there is doubt about whether the firm has or needs to have an approved medicated feed mill license (Form FDA 3448).

D. Veterinary Feed Directive Drugs (VFD)

Inspections of feed mills should determine compliance with the published requirements for those drugs identified as VFD Drugs. Only two VFD drugs, Tilmicosin, 21 CFR 558.618, and Florfenicol, 21 CFR 558.261 are approved at this time. Paperwork requirements particular to this regulation include verification of notification letter, acknowledgement letters provided by other companies and copies of all VFD orders (original copy) received. Surveillance inspections may extend to

non-registered sites and to the veterinarian, particularly when following or tracing the use of VFD feeds. As with any drug in feed, attention should be given to labeling to assure proper directions and cautions are included. Review records and compare tonnage of feed produced to see if it matches what is listed on the VFD. Also, review information concerning the disposition of any leftover VFD feeds. If warranted, audit the paper trail for at least one VFD feed. If a VFD feed results in the finding of an illegal tissue residue, distribution chain tracking may start at the user level.

E. Registration Cancellation and Medicated Feed Mill License Voluntary Withdrawal

Provide the form letter (**Attachment B**) to a firm to withdraw its Medicated Feed Mill License without prejudice and to cancel its drug registration. Forward the completed copy to CVM, HFV-226.

F. Program Interactions

Refer to Compliance Program 7371.005, Type A Medicated Articles for guidance on firms that manufacture Type A Medicated Articles. Time should be charged accordingly.

Refer to Compliance Program 7371.009, BSE/Ruminant Feed Ban Inspections, for guidance on inspections/investigations of renderers, protein blenders, licensed and unlicensed feed manufacturers, distributors, retailers, on-farm feed mixers, and ruminant feeders.

PART III - INSPECTIONAL

INSPECTIONAL OPERATIONS

General Information

An important responsibility of all animal feed manufacture is to assure that the feed produced, whether medicated or non-medicated, is truthfully labeled, does not contain unsafe additives or contaminants, and, if drugs are present, they are safe and effective for their intended use. Medicated feeds should be properly mixed to assure that their products comply with the requirements of CGMP regulations to ensure animal feeds manufactured are safe, have labeled identity and strength, and meet quality and purity characteristics they should possess with respect to their drug content.

The main focus for the Feed Manufacturing Compliance Program is the inspectional and regulatory coverage of medicated feed manufacturers to determine if they are in compliance with the CGMP requirements

Firms planning to manufacture medicated feeds that require a medicated feed mill license must comply with the requirements of 21 CFR 515 and 21 CFR 225.1 - 225.115, and be registered in accordance with 21 CFR 207. FDA determines whether a medicated feed firm is complying with the requirements of the CGMP regulations by inspecting the firm's controls, operations and facilities at periodic intervals. Registered firms are to be inspected at least once every two years.

Free-choice administration of animal drugs in feeds covers feeds placed in feeding areas that are not intended to be consumed fully at a single feeding or do not constitute the entire diet of the animal (e.g., lick tanks, blocks, mineral mixes, etc.). A new animal drug administered to animals as a component of free-choice feeds must be the subject of an approved NADA (21 CFR 510.455(b). Additionally, an approved medicated feed mill license is required for the use of all drugs (Category I and II) in the manufacture of all free-choice medicated feeds (21 CFR 510.455(f).

21 CFR Section 558.5 states that the labeling of a drug product to provide for its use in a liquid Type B Medicated Feed causes the drug to be a new animal drug for which an approved NADA is required pursuant to section 512(b) of the FFD&C Act.

The addition to a liquid Type B Medicated Feed of any Category II drug or any Category I drug whose formula or specifications is not published in the CFR causes the Type B feed to become an animal feed bearing or containing a new animal drug for which an approved medicated feed mill license is required pursuant to section 512(m) of the Act.

1. CGMP Information

a. Surveillance Inspections

Surveillance inspections are conducted to determine whether a firm is substantially in compliance with CGMP requirements. Overall compliance is determined by review of certain portions of the firm's operations using Form FDA 2481 (**FDA Form 2481**) as a guide to recording observations and evaluating CGMP compliance. With the exception of the identifying firm data and the VFD data, the remainder of the FDA 2481 refers to the more stringent cGMPs (21 CFR 225.10-225.115, those used by licensed feed mills), and is not for use in inspecting non-licensed or non-medicated feed manufacturers

EACH "NO" ANSWER ON THE FORM FDA 2481 SHOULD BE FULLY EXPLAINED (AND DOCUMENTED, IF POSSIBLE) IN THE NARRATIVE SECTION. ITEMS NOT COVERED ON THE FORM FDA 2481 SHOULD BE MARKED AS N/C (NOT COVERED). Documentation can be accomplished by various means such as collection of photocopies of the records in question, photography, sample collection, obtaining of affidavits, etc. All requests for photocopies, as with any other inspection, must be reasonable. Also, reading the Investigations Operations Manual (IOM) about photography and the associated explosion hazards is highly recommended.

The key CGMP elements are designated on Form FDA 2481 with an asterisk. All items on the checklist are to be covered. However, greater importance should be placed on the asterisked items. These items should be addressed and adequately documented in the narrative portion of the form to enable the District reviewer to classify the inspection and determine appropriate monitoring and follow-up at the firm.

A suggested inspectional approach is to select at least two drugs and trace these drugs through the system, from receipt of the raw material to shipment of the medicated finished feed. Determine if the establishment can 1) locate and recall its product, and 2) determine if a product can be traced back through the distribution chain to its production.

When needed, CVM will request a pre-approval inspection. The investigators performing these inspections determine whether the firm has the necessary knowledge of CGMP requirements, adequate equipment, drug receipt and inventory controls, formula and production instructions/records, and sampling and assay plans to substantially comply with the CGMP requirements. Although CGMP requirements will be the area of emphasis for pre-approval inspections, all items on the checklist are to be covered.

Surveillance inspections can be converted to compliance inspections when significant objectionable deviations from CGMP requirements are encountered. ***(See the asterisked items on the Form FDA 2481.)***

b. Compliance Inspections

Compliance inspections are conducted to evaluate a firm's compliance with the provisions of the CGMP regulations and to document inspectional observations supporting possible enforcement action.

Compliance CGMP inspections are to be conducted at firms where previous CGMP inspections have been classified by the District office as OAI (District Decision Data Code "A") or when following up on a report of a violative tissue residue.

c. CGMP Guidance

Some background information as well as interpretation of CGMP regulations for the asterisked items in the Form FDA 2481 are listed below. Numbers in parenthesis refer to sections of Title 21 CFR.

Subpart B - Construction and Maintenance of Facilities and Equipment

Buildings (225.20) - Facilities used for the storage and mixing operations for medicated feeds shall be maintained in a reasonably clean and orderly manner. Accumulated dust or residues will be considered objectionable when there is a likelihood that the material could contribute to significant contamination of animal feeds.

Equipment (225.30) - All equipment used in the manufacture of medicated feed shall be suitable for its intended use and shall have the capability to produce a homogeneous medicated feed of the intended potency. The capability of the mixing equipment should be demonstrated upon installation through some means by using, for example, a mixer study that tests for the drug or micro-ingredient of low-inclusion, the salt test or any other suitable test. Procedures to monitor the capability of the equipment to produce a homogeneous medicated feed of the intended potency should be developed and implemented.

Scales and metering devices shall be of suitable size and accuracy to make accurate measurements of the critical feed components. Test the accuracy of the drug ingredient scales with a known calibrated weight**.** All scales and metering devices should be tested for accuracy upon installation and at least once per year subsequent to that installation **(asterisked item 25)**. Inaccurate measuring

devices can significantly affect the potency of the finished medicated feed.

Some firms may use pre-weighed packages of drug ingredients. If only pre-weighed packages are used, then the questions concerning scales on Form FDA 2481 are not applicable (N/A) and should be so marked. However, determine and report what controls the firm has to assure that the proper number of packages are used in a specific lot of medicated feed (**asterisked item 65**).

Use of the work/storage areas and equipment for other purposes (225.35) - Determine if Type A Articles and medicated feeds are stored and handled in a manner to prevent mix-ups and contamination in the case of leakage or breakage. When other products such as pesticides and industrial chemicals are stored and/or handled in the same general facility, determine if the physical separation is adequate to avoid mix-up and contamination problems **(asterisked item 30**).

Subpart C - Product Quality Control

Drug Components (225.42) - A firm is required to inspect and record the inspection of all incoming shipments of drug components for medicated feeds to assure that packages are intact and properly identified and the drug contents are not damaged. Unacceptable containers are to be returned to the shipper and a record of such transaction is to be maintained in the firm's receipt record files.

Type A Medicated Articles shall be stored and handled in a manner to prevent mix-ups and contamination that may adversely affect finished animal feeds. **Asterisked item 40** deals with how drugs are handled by a medicated feed firm. Failure to adequately identify, store, handle and control drug components could cause serious defects in finished animal feeds, and could adversely affect animals and humans consuming the edible products thereof.

A record for each lot of drug component received shall be established and maintained so that adequate investigations of product defects can be accomplished and satisfactorily resolved.

A firm must establish and maintain a daily inventory record for each drug used. This record is required to show when and which drug lot was used in specific batches or production runs of medicated feed; how much was used; and how much remains in inventory after each daily use in order to cross-check drug usage with production records. The inventory records are intended to serve a useful quality control function to detect errors in drug usage. The term "daily" means each 24-hour period that a drug component is used. The inventory record may be several records that interrelate to provide the needed information. An individual at

the manufacturing site should be able to demonstrate how the system works. **Asterisked items 45 and 47, a, b, c and d,** deal with daily drug inventory procedures. These are critically important elements. For additional guidance see Compliance Policy Guide Section 680.200.

Laboratory Controls (225.58) - The firm's assay procedures and sampling schedules shall conform to license requirements, 225.58(b)(1), which requires at least three representative samples of medicated feed containing each drug or drug combination be collected and assayed at periodic intervals during the calendar year, unless otherwise specified. If a medicated feed contains a combination of drugs, only one need be analyzed each time, provided the one tested is different from the one(s) previously tested. An exception is made for a medicated feed manufactured from a fixed combination Type A Medicated Article. One or all of the drugs in combination may be analyzed and if one or all meet specifications, then the medicated feed is considered to be correctly manufactured. If one drug is analyzed in the combination, it does not have to be a different one each time; that is, a marker drug can be used. Assays conducted by State laboratories may be included when considering whether the requirement for three assays is being met. The requirement to assay the first medicated feed batch using the drug means the first batch of that medicated feed ever produced by the firm. This is to provide timely evidence of the firm's capability to manufacture that particular medicated feed. **Asterisked item 51** on Form FDA 2481 deals with the firm's adherence to the assay requirements.

Analysis of medicated feed provides some measure of performance of the manufacturing process. The daily drug inventory procedure and yield reconciliation is considered an effective control mechanism in identifying possible errors in the immediate manufacture of medicated feeds. Nevertheless, when the results of sample analysis reveal that a drug level in a batch of medicated feed is out-of-limits, adequate investigation and corrective action shall be undertaken by the firm to comply with 225.58(d) and (e). **Asterisked items 52 and 55,** deal with these requirements. Such investigation shall be documented.

Adequate investigation and corrective action would include a recheck of the critical manufacturing steps. For example:

- Examine the daily drug inventory records to determine whether the correct Type A Medicated Article and level was used.
- Verify formula for correct Type A Medicated Article, potency, and use level.
- When appropriate, check for misnumbered codes that were applied by the firm to the Type A Medicated Article.
- Check for production yields of target, preceding, and subsequent batches.
- Depending upon the nature and precedence of a drug assay problem, the firm

may choose to assay a split portion of the sample, assay the Type A Article, and/or review the problem with the Type A Article manufacturer.

- A determination as to whether proper control procedures were followed.
- Place current inventory from target batch on hold and cease production of target feed pending conclusion of investigation.

In all cases where assay results show drug levels out-of-limits, the firm shall conduct a thorough investigation (21 CFR 225.58(d)). One of the reasons for an investigation is to determine whether or not a manufacturing error has taken place. Assays are considered a check on procedures and controls, and unexpected and/or extreme findings may indicate a serious problem. Repeated instances of out-of-limits assays of the same drug for sampling, handling, and method performance should be investigated further, since the expectation is this would not be a routine occurrence.

With respect to a medicated feed containing a combination of drugs from a single fixed Type A Medicated Article and an out-of-limits drug level involving methodology that might be affected by feed component or matrix interference, the firm may, at its discretion, assay the retained portion of the sample for both that drug and the second drug having a definitive assay method. Where a medicated feed with a drug level reported out-of-limits involving a problematic method cannot be confirmed by other methodology on the second assay, greater reliance may be placed upon the results of the record investigation. Confirmed out-of-limits results, either by analysis or records are to be taken seriously and, under normal circumstances, indicate that the batches or production runs are to be removed from the market. All confirmed out-of-limit assays of a medicated feed that has been distributed, and any circumstances/assays that suggest a problem with the Type A Medicated Article or the NADA drug, such as sub- or super-potency, must be reported to CVM by the firm (21 CFR 510.301(a)(2) and 21 CFR 225.58(d)).

The firm must have a written record of the complete investigation and all analytical results, the conclusion reached, and the action taken. Review the record to determine if the samples were analyzed as required, whether the investigation was complete, if any remaining feed from the batch was held pending completion of the investigation, and whether the conclusion and action appears appropriate. All out-of-limits assays along with the subsequent investigation and resolution should have been reported to CVM (HFV-226).

Equipment Clean-out Procedures (225.65) - The firm must have written procedures to prevent unsafe carry-over of drugs into subsequent production of animal feeds. These procedures may include flushing, physical clean-out, sequencing or any other procedure which has been shown to prevent carry-over of

unsafe drug residues into animal feeds.

Determine whether the firm's standard operating procedures appear adequate to prevent unsafe carry-over of drug residues into other feeds and whether the firm follows the written procedures. If the adequacy of the firm's clean-out procedures are questioned, follow Compliance Policy Guide (CPG) 680.500. See **Asterisked item 32**.

Flushing is the process of using an ingredient, usually an abrasive-type material such as corn, soybean meal, peanut hulls, etc., after the production of a batch of feed, through the manufacturing equipment and associated handling equipment (e.g. conveyors) for the purpose of cleaning out any drug residue. If the firm uses a flushing procedure to prevent unsafe carry-over, determine and report how the firm has established the kind and quantity of flush material to be used, and how the flush materials are used, recovered, stored, and identified for subsequent use. If there is potential that use of flush materials may result in unsafe contamination of feeds, include the observation on the FDA 483 (Inspectional Observations). See CPG 680.500 for guidance.

Physical clean-out of medicated feed mixing and handling equipment may include vacuuming or sweeping. The regulation also provides for washing; however, due to other feed and environmental safety questions and concerns, washing is not generally utilized. Physical clean-out procedures, if used by a firm, should be determined by the firm to be effective to prevent unsafe contamination of animal feeds.

Sequencing allows the predetermined disposition of residual drug carry-over. As discussed in Compliance Policy Guide 680.600, sequencing should be based upon a valid rationale to prevent unsafe contamination in subsequently produced animal feeds. For instance, a sequencing procedure that allows for mixing a swine finishing feed after a medicated feed containing sulfamethazine is not acceptable, since it has been shown that a very low concentration of sulfamethazine consumed up to slaughter can result in illegal residues in edible tissues. It is also unacceptable to mix a horse feed subsequent to mixing a monensin or lasalocid-containing feed due to severe or fatal effects of these drugs in horses.

Subpart D - Packaging and Labeling

Blue Bird Labels

Blue Bird labels serve as the source of information that must appear on the actual medicated feed labels. Current NADA approved (Blue Bird) Type B and/or Type C medicated feed labeling for each Type B and/or Type C medicated feed being manufactured should be in the possession of the FDA licensed medicated feed manufacturing facility prior to receiving the Type A Medicated Article. Possession includes either having the Blue Bird label on the premises or having it available electronically by computer or obtaining a copy by FAX. In assessing compliance with this requirement, consider the firm's overall ability to generate accurate medicated feed labels.

Labeling (225.80) - Labeling (including placards and invoices when used in lieu of bag labels) must contain adequate directions and warnings for the safe and effective use of medicated feeds. Check labeling for proper withdrawal times (verify using label of approved NADA). Determine whether mixer-feeders are knowledgeable of and following proper withdrawal times. If there are discrepancies with the labeling, check to see if the Blue Bird labels are accessible. **Asterisked items 61 and 62 a, b, c** deal with the firm's labeling practices.

Subpart E - Records and Reports

Master record file and production records (225.102) - Master record files shall contain, among other things, the name of the medicated feed, a complete formula, a copy or description of approved labeling, and manufacturing instructions. **Asterisked items 65 a, b, c, d, e, and f** deal with the firm's master file records. Failure to comply with the minimum master file requirements could result in production of medicated feeds which do not meet specifications.

Some firms develop/amend their feed formulas at one location and transmit them via computerized systems to a number of feed manufacturing facilities. Most of the time, it has been difficult for the investigator to verify that each master file record has been checked, dated, and signed or initialed by a qualified person. When this scenario is encountered, mark **item 74** "No", indicating why in the narrative section. Although this is a non-asterisked item, the information should be provided in the Establishment Inspection Report (EIR) for possible inspection of the site that develops/amends the formulas.

Production records for each batch or production run of medicated feed shall include information to accurately reflect:

- The date of production;
- Quantity and name of drug components used;
- Theoretical and actual quantity of medicated feed produced;
- Evidence that a responsible individual has reviewed the records to determine whether all production steps have been performed;
- Reference to the specific formula or master file used.

The records must provide enough information to identify the lot or lots of drug components used in the medicated feed so that adequate trace back or recalls can be performed if any question regarding drug safety or efficacy develops and to cross-check the accuracy of drug inventory usage records.

Review a representative number of production records for correct drug levels, agreement with the master formula and completion of all production steps. **Asterisked item 70, a, b, c, d, e, f and g** deals with production records.

Custom formula medicated feeds made to the specifications of the customer must conform to approved drug levels, labeling, and indications. Master record file information and production record information may be combined on the customer's purchase order and the manufacturer's invoice; however, complete required information must be included to comply with 225.102(b)(3).

Distribution records (225.110) - Distribution records must contain enough information to enable the manufacturer to trace specific batches of medicated feeds should there be any question regarding drug safety or efficacy e.g., complaints, recalls, etc. **Asterisked item 81** deals with the adequacy of distribution records.

Complaint file (225.115) - A medicated feed firm must maintain a complaint file at the plant. This file should contain, at the very least, any complaint on the drug's efficacy or safety in feed. Determine whether such a file exists and whether the firm's procedure for evaluation and corrective action is adequate.

Determine whether the firm is aware of the commitment in the approved medicated feed mill license regulation for timely filing of experience reports with CVM concerning medicated feeds and whether appropriate and necessary reports have been submitted. Note that the firms are obligated to report to CVM whenever a distributed lot of medicated feed fails to meet the specifications provided for in the approved NADA (21 CFR 510.301(a)(2)). When determining if specifications have been met, consider the firm's investigation and evaluation while focusing on the significance of the complaint.

2. Other Drug Related Issues

A. Manufacture of Medicated Feed Without The Required Feed Mill License

If a feed mill has a Type A Medicated Article requiring an approved medicated feed mill license in its inventory and the mill does not have an approved medicated feed mill license, the receipt of the drug, the mixing of the drug into medicated feed, and the distribution of the medicated feed are violations that warrant regulatory action. The manufacturer of the unapproved medicated feed causes the feed to be adulterated. The shipper of the drug causes the drug to be adulterated if the receiver and user do not have the required approved medicated feed mill license for such use (Section 501(a)(2)(b) of the Act).

After authorization from your supervisor, perform a follow-up investigation at the shipper of the Type A Medicated Article. Complete documentation of the responsibility and the violation may support regulatory action against both the consignee/user and the shipper/distributor. Document (e.g., affidavits, freight bills, receiving tickets) shipments of Type A Medicated Articles requiring an approved medicated feed mill license from the distributor to unauthorized consignees, including the consignee/user mill just inspected.

If a medicated feed mill license applicant manufactures unapproved medicated feed, the license approval shall be refused. (See 21 CFR 515.21(a)(3)). If a licensed feed mill manufactures unapproved medicated feed and if the facility does not discontinue that manufacturing within a reasonable time, then it shall be considered as a reason to revoke the license. (See 21 CFR 515.22 (e)(4)).

Fully document the mixing and distribution of unapproved drugs or the manufacture and distribution of medicated feeds containing unapproved combinations of new animal drugs. The Agency's extra-label policy use does not apply to the manufacture of medicated feeds.

Investigators should also look for other non-CGMP violations such as the use of drugs for medicated feeds from unapproved sources, the use of soluble powders intended for use in drinking water and bulk drug substances, and the illegal sale or distribution of veterinary Rx drugs. These types of violations should be documented in the EIR.

B. Veterinary Feed Directive Drugs (VFD)

If firms handle VFD drugs, audit the paper trail for at least one VFD feed manufactured by the firm. Records for VFD orders should be checked to

determine if a copy of the VFD issued by the veterinarian was retained and whether all mixing and cautionary instructions issued by the veterinarian were followed.

Fully document any deviations from VFD recordkeeping requirements by documentary sample collection. If a trace-back of a VFD feed is required, the District initiating the trace will be responsible for tracking its progress and issuing assignments.

Review production records and compare tonnage of feeds produced with the amount to be produced listed on the VFD. Also review information on the disposition of any leftover VFD feeds. Pay attention to equipment clean-out procedures. See **item 15** on Form FDA 2481.

Questions concerning the VFD requirements are addressed in Guidance for Industry #120.

3. Sampling of Medicated Feeds

The collection of evidence to substantiate and document violations is a necessary element for an enforcement action. Official samples (documentary and/or physical) should be collected whenever the investigator observes significant violative conditions. Official samples document violations of the FFD&C Act and FDA jurisdiction. At a minimum, a documentary sample should be collected for any violative **asterisked** item on Form FDA 2481.

Physical samples of bagged or bulk complete feeds are collected to demonstrate residue carry-over, potency or cross contamination problems.

a) **For bagged complete feed:**
Collect a total sample of not less than 2.3 KG (5 lbs.) from each lot. Collect 454 grams (1 lb.) subs, sampling all available bags from lots of 10 bags or less. If the lot size is greater than 10 bags, collect 454 grams (1 lb.) from each of 10 bags selected at random.

b) **For bulk complete feed**:
Collect at least 10-454 gram (1 lb.) subs from different points in the bulk lot to obtain a minimum total sample of 4.5 kg. (10 lbs.)

Investigational (INV) Samples may be collected to document that residues may have been carried over into the finished product. For these samples, collect at least 900 grams (2 lb.) of static residual material from the manufacturing equipment and correlate these with finished feed samples. When collecting INV

samples, do so only at firms mixing Category II drugs where there is a reasonable probability of cross-contamination.

The criteria for collecting cross-contamination samples during medicated feed inspections to demonstrate unsafe contamination are as follows:

- There are no procedures to prevent drug carry-over
- The flushing procedure and/or the volume of flush material does not appear adequate
- The firm's physical clean-out appears inadequate
- The sequencing plan and procedures are inadequate (See CPG 680.600)

Additionally, collect samples if any of the below conditions exist:

- Collect samples at firms supplying feed to consignees that have experienced tissue residues or adverse reactions in their animals.
- Collect samples when looking for source of contamination.

Samples for potency are compliance (i.e., for cause) samples; no surveillance samples are collected for potency.

Note: ***Contamination not related to drug use should be covered under the Feed Contaminants Program 7371.003*****.**

4. General Sampling Precautions/Additional Information

See the Investigations Operations Manual (IOM) sampling schedule that pertains to medicated animal feeds for sample sizes, potency and drug carry-over determinations in feed, etc..

- Collect potency samples and cross-contamination samples in whirl-pak plastic bags. DO NOT fumigate samples intended for potency analysis, drug carry-over or cross contamination analysis. **DO NOT USE PAPER BAGS. STORE IN ACCORDANCE WITH LABEL INSTRUCTIONS.** When sampling bagged complete feeds, insert the trier the full length of the bag.
- Clean the trier between sampling different lots of complete feeds.
- Place subs in whirl-pak bags. **DO NOT USE PAPER BAGS**.
- Always store product according to label instructions.

5. Medicated Feed Mill Sample Preparation and Shipment

a. Submit FDA samples to the Denver (DEN-DO) Laboratory with a copy of the

product labeling. Samples should be analyzed both for antibiotics and other drugs. Telephone the Denver Lab prior to shipment at 303-236-3061. Address samples to:

Food and Drug Administration
6th and Kipling St.
Building 20
Denver Federal Center
Denver, CO 80225-0087

b. State officials should submit their samples to the appropriate State laboratory unless instructed otherwise.

PART IV - ANALYTICAL

A. Analyzing Laboratories

1. FDA Laboratories - All analyses will be done by Denver Laboratory (DEN-DO).

2. State Laboratories - State laboratories will prepare and analyze their own samples unless instructed otherwise.

B. Analysis

1. Sample Analysis

   Conduct all analyses for potency on the composite portion before analyzing individual subs. Analysis for drug carry-over is to be done on individual subs.

   Analyze individual subs only when results on individual subs are deemed necessary to support regulatory action. In general, analyze a minimum of five subs to demonstrate degree of sample homogeneity.

2. Drug Contaminant Analysis

   Questions concerning the technical or scientific aspects of analysis should be directed to the Division of Field Science, HFC-140, 301-827-7606. Questions concerning regulatory action levels or potentially hazardous levels should be directed to Division of Compliance, HFV-230, 301-594-1785.

3. Drug Potency Analysis

   Analyze feed samples for potency of drug components as specified on the collection report.

C. Methodology

Sample Preparation for Drugs Other Than Antibiotic Drugs

- Prepare a composite by thoroughly mixing together equal portions (usually 50-100g) from each subsample. Divide the prepared composite sample into two equal portions (one is the 702(b) portion) and store under seal in air-tight containers.

- Use the procedure described in the Association of Official Analytical Chemists (AOAC), 17th ed. 950.02, to prepare the composite sample for analysis.

- When possible, use the AOAC methods. If the product is the subject of an approved NADA, and is found violative by a method other than one in the NADA, the feed sample must be examined by methods specified in the approved NADA. Non-official methods used for regulatory analysis must be validated, reporting method attributes.

PART V - REGULATORY/ADMINISTRATIVE FOLLOW-UP

A. FEDERAL/STATE LIAISON

When violative feeds are encountered, advise State feed control officials. Cooperating officials often have the interest and authority to correct violative conditions expeditiously. FDA action concerning the medicated feed mill license may also still be needed.

Arrangements should be made with States conducting feed inspections under this program to assure that the Districts are notified promptly when violative conditions are encountered that will result in an OAI inspection classification.

B. INTERAGENCY LIAISON

If conditions are found that have a reasonable potential for causing violative drug residues, notify Food Safety and Inspection Service/United States Department of Agriculture (FSIS/USDA) to sample animals receiving the suspect medicated feed. See Federal Cooperative Agreements Manual 225-85-8400 for the Memo of Understanding (MOU) with USDA (FSIS and Agricultural Marketing Service (AMS)) and Environmental Protection Agency (EPA).

C. VOLUNTARY ACTION INDICATED

Seek voluntary correction of CGMP deviations that are minor, non-repetitive, or limited in scope. When CGMP deviations are isolated occurrences and not representative of the common practice of the firm, they usually would not warrant refusal to approve a license or regulatory action. However, if reasonable voluntary compliance efforts fail to correct a continuing pattern of CGMP deviations, formal administrative/regulatory action should be considered using the Administrative/Regulatory Sanctions in Part V section D of the program.

D. ADMINISTRATIVE/REGULATORY SANCTIONS

NOTE:
All Warning Letter proposals will be reviewed by the centers until further notice. District offices should review current instructions regarding the review and processing of Warning Letters prior to issuance.

1. CGMP Deviations

Recommend formal administrative action and/or regulatory action when CGMP violations demonstrate that the methods, facilities, or controls being used by the firm cause an actual or probable adverse impact on the safety, identity, strength, quality, or purity of the finished product. These significant CGMP violations support an OAI inspection classification. The following course of follow-up action should be considered:

a. On the initial CGMP inspection classified OAI, typically a Warning Letter would be issued. (See **Attachment C** for model Warning Letter.) The District has the discretion to determine whether a Warning Letter is appropriate based on the circumstances of the specific case. Each letter concerning OAI inspections must contain the following elements:

(1) Approval of medicated feed mill license will be refused until the CGMP deviations are corrected. (This applies to unlicensed mills only.)

(2) A statement that the letter constitutes official notice of CGMP violations as required under Section 512(m)(4)(B)(ii) of the Federal Food, Drug, and Cosmetic Act.

NOTE: Issuance of the official notice under Section 512(m)(4)(B)(ii) of the FFD&C Act, (item a (2) above), is a prerequisite for withdrawal of the feed mill license.

b. If the CGMP re-inspection is violative and classified OAI, recommend:

(1) issuance of a notice of opportunity for a hearing (NOOH) proposing withdrawal of existing license and/or

(2) regulatory action, e.g., injunction and/or mass seizure of feeds, medicated feeds and drug components.

c. If CGMP deviations are identified which do not support an OAI classification, the District has the discretion to determine what type of follow-up (e.g., meeting with the firm) is appropriate and who should be delegated the responsibility for conducting such follow-up activity.

Examples of significant CGMP violations that warrant OAI classification and the course of follow-up action include:

- Failure to conduct adequate clean-out procedures which have or could result in unsafe contamination of the finished product.

- Scales or metering devices used to determine the amount of drug ingredient in the product are inaccurate or are operating in a manner that has caused or could be expected to cause incorrect or erratic drug levels in the medicated feed.
- Lack of daily drug inventory records or failure to make a daily comparison between the actual amount of drug used and the theoretical amount of drug used or failure to take corrective action when significant discrepancies are detected.
- A pattern of failure to perform medicated feed assays according to the schedule in CFR 225.58.
- Lack of follow-up action to determine and correct, where feasible, the cause of medicated feeds not meeting assay specifications.
- Failure to properly label medicated feeds; for example, lack of withdrawal instructions on labeling or operating in a manner that would favor a label mix-up.
- Failure to have master records or production records, or such records are lacking elements that can reasonably be expected to cause an adverse effect on the finished product.

2. Non-CGMP Violations

Below are several examples of non-CGMP violations that warrant issuance of Warning Letters as the initial action:

a. Failure to have an approved FDA medicated feed mill license when required.
b. Use of unapproved drugs, or unapproved combinations or levels of approved drugs.
c. Failure to register as a drug manufacturer when using drug(s) that require(s) a medicated feed mill license (See CPG 660.100 - Failure to Register).
d. Illegal distribution of a Type A Medicated Article.
e. Failure to adhere to the VFD requirements.
f. Failure to maintain or have access to approved Blue Bird labels, if there is a failure to properly label medicated feeds.

*Center concurrence is needed prior to the issuance of a Warning Letter. (See Chapter 4 of the FDA Regulatory Procedures Manual).

3. Violative Surveillance Sample

If sizeable quantities of the violative medicated feed remain, discuss recall strategy with the firm. If only a small quantity remains, a direct reference Warning Letter will issue to the manufacturer of the feed. Seizure action must have concurrence of the Center.

4. Import

Detain or refuse entry of medicated feeds that appear to be in violation of the FFD&C Act and

regulations. Release, with comments, feeds with minor violations.

E. INSPECTION CLASSIFICATION AND MEDICATED FEED MILL LICENSE APPROVAL/DENIAL

Firms with CGMP deviations as described under item D, **ADMINISTRATIVE/ REGULATORY SANCTIONS**, will be classified under PAC 71004 as Official Action Indicated (OAI). The district office will advise both these firms and CVM that approval of pending and future medicated feed mill licenses will be refused until the CGMP deviations are corrected.

Firms with CGMP deviations as described under item C, **VOLUNTARY ACTION INDICATED**, should be classified under PAC 71004 as either NAI, or VAI. Medicated feed mill license approval by CVM will not be affected by these classifications.

PART VI - REFERENCES, ATTACHMENTS AND PROGRAM CONTACTS

A. APPLICABLE REFERENCES OR AIDS

1. Investigations Operations Manual: Chapter 4 - Sampling, and Chapter 5 – Establishment Inspection
2. 21 CFR Part 225, Current Good Manufacturing Practice Regulations for Medicated Feeds
3. 21 CFR Part 515, Medicated Feed Mill License
4. 21 CFR Part 558, New Animal Drugs for Use in Animal Feeds
5. 21 CFR Part 558.6, Veterinary Feed Directive
6. 21 CFR Part 11, Electronic Records; Electronic Signatures
7. Official Publication (current edition), Association of American Feed Control Officials, Inc.
8. Official Methods of Analysis of the Association of Official Analytical Chemists, current edition
9. CPG 615.200, Proper Drug Use and Residue Avoidance by Non-Veterinarians
10. CPG 625.500, Failure to Register
11. CPG 680.200, CGMP Regulations for Medicated Feeds--Daily Inventory Requirements
12. CPG 680.500, Unsafe Contamination of Animal Feed from Drug Carryover
13. CPG 680.600, Sequencing as a Means to Prevent Unsafe Drug Contaminants in the Production, Storage, and Distribution of Feeds
14. CPG 666.100, Alternate Feeding of Different Medicated Feeds
15. CPG 689.100, Direct-Fed Microbial Products
16. CPG 160.100, Regulatory Actions and Small Business
17. MOU with USDA, Food Safety and Inspection Service and Agricultural Marketing Service and EPA *MOU 225-85-8400 - MOU between FDA, FSIS, and EPA regarding regulatory activities concerning residues of drugs, pesticides and environmental contaminants in foods*
18. Trade Guides such as Feed Additive Compendium, The Miller Publishing Co., Minneapolis, MN.
19. Animal Drug Availability Act of 1996
20. FDA/CVM Guidance on Veterinary Feed Directive, #120
21. Guidance For Industry: GMP'S For Medicated Feed Manufacturers Not Required to Register and Be Licensed with FDA
22. Regulatory Procedures Manual

B. FORM(S)/ATTACHMENTS

Attachment A - Drug Category List (I and II)
Attachment B - Sample Form Letter to Voluntarily Withdraw Approval of Medicated Feed Mill License
Attachment C - Model Warning Letter

C. PROGRAM CONTACTS

1. ORA Contacts

- FDA personnel should direct inspection inquiries to James Dunnie, Division of Field Investigations/Domestic Group, HFC-130, on 301-827-5652; e-mail address: james.dunnie@fda.hhs.gov
- State personnel should direct inspectional inquiries to the District Program Coordinator or the State/Federal Contract Co-Project Officer on 301-827-2907.
- Direct questions about methodology to the Division of Field Science, HFC-140, on 301-827-7606.
- Direct resource inquiries to Program Planning & Workforce Management Branch, HFC-41 on 301-443-3330.

2. Center Contacts

Program and Administrative Inquiries
Isabel Pocurull, Program Monitor
Division of Animal Feeds
Medicated Feeds Team, HFV-226
E-Mail Address:
isabel.pocurull@fda.hhs.gov
Phone: 240-453-6853

GMP and Labeling Inquiries
Dragan Momcilovic, Medicated Feed Specialist
Division of Animal Feeds
Medicated Feeds Team, HFV-226
E-Mail Address:
dragan.momcilovic@fda.hhs.gov
Phone: 240-453-6856

Regulatory Inquiries
Paul Bachman
Division of Compliance
E-Mail Address:
Paul.bachman@fda.hhs.gov
Phone: 240-276-9225

Program Manager
Jo Gulley, Team Leader
Medicated Feeds Team, HFV-226
Division of Animal Feeds
E-Mail Address:
jo.gulley@fda.hhs.gov
Phone: 240-453-6858

Category I			
Drug	**Assay Limits[1] Type A**	**Type B Maximum (200X)**	**Assay Limits Type B/C[2]**
Aklomide		22.75 g/lb (5.0 %)	85-120
Amprolium with Ethopabate		22.75 g/lb (5.0%)	80-120
Bacitracin methylene disalicylate		25.0 g/lb (5.5%)	70-130
Bacitracin zinc		5.0 g/lb (1.1%)	70-130
Bambermycins		800 g/ton (0.09%)	80-120/70-130
Chlortetracycline		40.0 g/lb (8.8%)	80-115/70-130
Coumaphos		6.0 g/lb (1.3%)	80-120
Decoquinate		2.72 g/lb (0.6%)	80-120
Dichlorvos		33.0 g/lb (7.3%)	90-120/80-130
Diclazuril		182 g/t (0.02%)	85-115/70-120
Efrotomycin		1.45 g/lb (0.32%)	80-120
Erythromycin (thiocyanate salt)		9.25 g/lb (2.04%)	<20 g/ton: 70-115/150-50 >20 g/ton: 75-125
Iodinated casein		20.0 g/lb (4.4%)	75-125
Laidlomycin		1 g/lb (0.22%)	90-115/85-115
Lasalocid		40.0 g/lb (8.8%)	Type B (cattle & sheep): 80-120 Type C (all) 75-125
Lincomycin		20.0 g/lb (4.4%)	80-130
Melengestrol acetate		10 g/ton (0.0011%)	70-120

[1] Percent of labeled amount

[2] Values given to represent ranges for either Type B or Type C medicated feeds. For those drugs that have two range limits, the first set is for a Type B medicated feed and the second set is for a Type C medicated feed. These values (ranges) have been assigned in order to provide for the possibility of dilution of a Type B medicated feed with lower assay limits to make Type C medicated feed.

Category I			
Drug	**Assay Limits[1] Type A**	**Type B Maximum (200 X)**	**Assay Limits Type B/C[2]**
Monensin		40.0 g/lb (8.8%)	Poultry: 75-125 Cattle : 5-10 g/ton 80-120 10-30 g/ton 85-115 Goats: 20 g/ton 85-115 Liquid Feed: 80-120
Narasin		7.2g/lb. (1.6%)	85-115/75-125
Nequinate		1.83 g/lb (0.4%)	80-120
Niclosamide		225 g/lb (49.5%)	80-120
Nystatin		5.0 g/lb (1.1%)	75-125
Oleandomycin		1.125 g/lb (0.25%)	<11.25 g/ton 70-130 >11.25 g/ton 75-125
Oxytetracycline		20.0 g/lb (4.4%)	75-125/65-135
Penicillin		10.0 g/lb (2.2%)	65-135
Poloxalene		54.48 g/lb (12.0%)	Liquid Feed: 85-115
Ractopamine		1.8 g/lb (0.4%)	80-110
Salinomycin		6.0 g/lb (1.3%)	80-120
Semduramicin		2.25 g/lb (0.50%)	80-110
Tiamulin		113.4 g/lb 3.5 g/lb (0.8%) 5&10 g/lb	90-115 70-130
Tylosin		10.0 g/lb (2.2%)	75-125
Virginiamycin		10.0 g/lb (2.2%)	70-130
Zoalene		11.35 g/lb (2.5%)	85-115

[1] percent of labeled amount

[2] Values given represent ranges for either Type B or Type C medicated feeds. For those drugs that have two range limits, the first set is for a Type B medicated feed and the second set is for a Type C medicated feed. These values (ranges) have been assigned in order to provide for the possibility of dilution of a Type B medicated feed with lower assay limits to make Type C medicated feed.

Category II			
Drug	**Assay Limits[1] Type A**	**Type B Maximum (100 X)**	**Assay Limits Type B/C[2]**
Amprolium		11.35 g/lb (2.5%)	80-120
Apramycin		7.5 g/lb (1.65%)	80-120
Arsanilate Sodium		4.5 g/lb (1.0%)	85-115/75-125
Arsanilic acid		4.5 g/lb (1.0%)	85-115/75-125
Carbadox		2.5 g/lb (0.55%)	75-125
Carbarsone		17.0 g/lb (3.74%)	85-115
Clopidol		11.4 g/lb (2.5%)	90-115/80-120
Famphur		5.5 g/lb (1.21%)	90-115/80-120
Fenbendazole		8.87 g/lb (1.96%)	75-125
Florfenicol		N/A	80-110
Halofuginone hydrobromide		272.0 g/ton (0.03%)	75-125
Hygromycin B		1200 g/ton (0.13%)	75-125
Ivermectin		1180 g/ton (0.13%)	80-110
Levamisole		113.5 g/lb (25%)	85-125
Maduramicin ammonium		545 g/ton (0.06%)	80-120
Morantel tartrate		66.0 g/lb (14.52%)	85-115
Neomycin Oxytetracycline		7.0 g/lb (1.54%) 10.0 g/lb (2.2%)	70-125 65-135
Neomycin Sulfate		100g/lb (22.0%)	70-125
Nicarbazin (powder)		5.675 g/lb (1.25%)	85-115/80-120

[1] Percent of labeled amount.

[2] Values given represent ranges for either Type B or Type C medicated feeds. For those drugs that have two range limits, the first set is for a Type B medicated feed and the second set is for a Type C medicated feed. These values (ranges) have been assigned in order to provide for the possibility of dilution of a Type B medicated feed with lower assay limits to make a Type C medicated feed.

Category II			
Drug	**Assay Limits[1] Type A**	**Type B Maximum (100 X)**	**Assay Limits Type B/C[2]**
Nicarbazin (granular) Narasin		5.675 g/lb (1.25%) 5.675 g/lb (1.25%)	85-115/75-125 85-115/75-125
Nitarsone		8.5 g/lb (1.87%)	85-120
Nitromide, Sulfanitran,		11.35 g/lb (2.5%) 5.65 g/lb (1.24%)	85-115 75-125
Nitromide, Sulfanitran, Roxarsone		11.35 g/lb (2.5%) 5.65 g/lb (1.24%) 2.275 g/lb (0.5%)	85-115 75-125 85-120
Novobiocin		17.5 g/lb (3.85%)	80-120
Pyrantel tartrate		36 g/lb (7.9%)	75-125
Robenidine		1.5 g/lb (0.33%)	80-120
Ronnel		27.2 g/lb (6.0%)	80-120
Roxarsone		2.275 g/lb (0.5%)	85-120
Roxarsone Aklomide		2.275 g/lb (0.5%) 11.35 g/lb (2.5%)	85-120 85-120
Roxarsone, Clopidol, Bacitracin methylene disalicylate		2.275 g/lb (0.5%) 11.35 g/lb (2.5%) 5.0 g/lb (1.1%)	85-120 80-120 70-130
Roxarsone, Monensin		2.275 g/lb (0.5%) 5.5 g/lb (1.2%)	85-120 75-125
Sulfadimethoxine, Ormetoprim (5/3)		5.675 g/lb (1.25%) 3.405 g/lb (0.75%)	85-115/75-125 85-115
Sulfadimethoxine Ormetoprim (5/1)		85.1 g/lb (18.75%) 17.0 g/lb (3.75%)	85-115/75-125 85-115

[1] Percent of labeled amount.

[2] Values given represent ranges for either Type B or Type C medicated feeds. For those drugs that have two range limits, the first set is for a Type B medicated feed and the second set is for a Type C medicated feed. These values (ranges) have been assigned in order to provide for the possibility of dilution of a Type B medicated feed with lower assay limits to make a Type C medicated feed.

Category II			
Drug	**Assay Limits[1] Type A**	**Type B Maximum (100 X)**	**Assay Limits Type B/C[2]**
Sulfamethazine, Chlortetracycline		10.0 g/lb (2.2%) 10.0 g/lb (2.2%)	80-120 85-125/70-130
Sulfaethoxypyridazine		50.0 g/lb (11.0%)	85-115
Sulfamerazine		18.6 g/lb (4.0%)	85-115
Sulfamethazine, Chlortetracyline, Penicillin		10.0 g/lb (2.2%) 10.0 g/lb (2.2%) 5.0 g/lb (1.1%)	80-120 85-125/70-130 85-125/70-130
Sulfamethazine, Tylosin		10.0 g/lb (2.2%) 10.0 g/lb (2.2%)	80-120 75-125
Sulfanitran, Aklomide		13.6 g/lb (3.0%) 11.2 g/lb (2.5%)	75-125 85-120
Sulfanitran, Aklomide, Roxarsone		13.6 g/lb (3.0%) 11.2 g/lb (2.5%) 2.715 g/lb (0.60%)	75-125 85-120 85-120
Sulfanitran, Aklomide, Roxarsone		13.6 g/lb (3.0%) 11.2 g/lb (2.5%) 2.27 g/lb (0.5%)	75-125 85-120 85-120
Sulfaquinoxaline		11.2 g/lb (2.5%)	85-115
Sulfathiazole, Chlortetracycline, Penicillin		10.0 g/lb (2.2%) 10.0 g/lb (2.2%) 5.0 g/lb (1.1%)	80-120 70-130 70-130
Thiabendazole		45.4 g/lb (10.0%)	>7% 85-115; <7% 90-110
Tilmicosin		18.2g/lb (4.0%)	85-115

[1] Percent of labeled amount.

[2] Values given represent ranges for either Type B or Type C medicated feeds. For those drugs that have two range limits, the first set is for a Type B medicated feed and the second set is for a Type C medicated feed. These values (ranges) have been assigned in order to provide for the possibility of dilution of a Type B medicated feed with lower assay limits to make a Type C medicated feed.

District Letterhead

Firm's Name & Address

Sir or Madam:

You are subject to the requirements of the Federal Food, Drug, and Cosmetic Act (the Act) and the regulations promulgated under it. If you hold a ***Medicated Feed Mill License*** (***Form FDA 3448***), the FFD&C Act and the regulations require you to register with the Food and Drug Administration (FDA) and make you subject to periodic inspections by FDA to verify your compliance with the Current Good Manufacturing Practice Regulations (CGMPs) for Medicated Feeds as published in the Code of Federal Regulations, 21 CFR Part 225.

However, if you no longer manufacture medicated feeds requiring a Medicated Feed Mill License and do not plan to do so in the future, you may cancel your registration and request the withdrawal of your Medicated Feed Mill License without prejudice. With the withdrawal of your Medicated Feed Mill License, you would be exempt from registration with the FDA.

Please be aware that if your Medicated Feed Mill License is withdrawn, you may not legally mix medicated feeds that are required to be manufactured in a Licensed Medicated Feed Mill. Should you subsequently wish to manufacture or mix a medicated feed that is required to be manufactured in a Licensed Medicated Feed Mill, you will be required to register the mill and submit a Medicated Feed Mill License (Form FDA 3448) application.

This inquiry is to aid the FDA in maintaining an inventory of only those firms actively engaged in mixing medicated feeds that require a Medicated Feed Mill License.

If these circumstances fit your situation, complete and return the enclosed letter to the Director of Compliance requesting the withdrawal of your Medicated Feed Mill License. We will forward a copy of your letter to FDA's Center for Veterinary Medicine for appropriate action.

Sincerely yours,

District Director

cc: HFV-226

Director of Compliance
District Address

Sir or Madam:

By authority of this letter, please do the following on my behalf (check all that apply):

_____Withdraw the approved **Medicated Feed Mill License** (Form FDA 3448)

_____Also, cancel my registration with the Food and Drug Administration

Medicated feeds that are required to be manufactured by a licensed medicated feed mill are no longer mixed by me. I understand that I must re-register with FDA and re-apply for a **Medicated Feed Mill License** if I should subsequently wish to manufacture or mix medicated feeds that are required to be manufactured by a licensed medicated feed mill.

Feed Mill Registration Number (CFN or FEI) _____

Medicated Feed Mill License Number _____

_____
Firm Name

_____
Address

_____
City, State Zip

Sincerely Yours,

_____
Name

_____
Title Date

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

RESPONSIBLE INDIVIDUAL, TITLE
FIRM NAME
FIRM MAILING ADDRESS

Dear _____:
An inspection of your medicated feed mill located at _____conducted by a Food and Drug Administration investigator on _____found significant deviations from Current Good Manufacturing Practice (CGMP) regulations for Medicated Feeds (Title 21 CODE OF FEDERAL REGULATIONS, Part 225). Such deviations cause feeds being manufactured at this facility to be adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act.

Our investigation found failure to **[Select one or more as appropriate for the inspection]** 1) flush or otherwise clean mixing equipment between batches of feeds medicated with different active drug ingredients; 2) failure to store packaged drugs in their original closed containers; 3) failure to maintain a daily inventory record for each drug used; 4) failure to conduct potency assays on at least three representative samples of each feed required to be manufactured by a licensed medicated feed mill at periodic intervals during the calendar year; and 5) failure to maintain complete master record files and production records.

The above is not intended as an all-inclusive list of CGMP violations. As a manufacturer of medicated and non-medicated feeds, you are responsible for assuring that your overall operation and the products you manufacture and distribute are in compliance with the law.

You should take prompt action to correct these CGMP violations, and you should establish procedures whereby such violations do not recur. Failure to promptly correct these CGMP violations may result in regulatory and/or administrative sanctions. These sanctions include, but are not limited to, seizure, injunction, and/or notice of opportunity for a hearing on a proposal to withdraw approval of your Medicated Feed Mill License under section 512(m)(4)(B)(ii) of the FFD&C Act and 21 CFR 515.22(c)(2). (This letter constitutes official notification under the law). Based on the results of the (date) inspection, evaluated together with the evidence before FDA when the Medicated Feed Mill License was approved, the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of

medicated feeds are inadequate to assure and preserve the identity, strength, quality, and purity of the new animal drugs therein. This letter notifies you of our findings and provides you an opportunity to correct the above deficiencies.

You should notify this office, in writing, within fifteen (15) working days of the receipt of this letter of the steps you have taken to bring your firm into compliance with the law. Your response should include an explanation of each step being taken to correct the CGMP violations and prevent their recurrence. If corrective action cannot be completed within 30 working days, state the reason for the delay and the date by which the corrections will be completed. Include copies of any available documentation demonstrating that corrections have been made.

Your response should be directed to _____ at the above address.

Sincerely yours,

District Director

cc: ADDITIONAL RESPONSIBLE INDIVIDUALS
HFV-230