SUBJECT:	IMPLEMENTATION DATE
Feed Manufacturing Compliance Program (FY 2000- 2005)	Upon Receipt
	COMPLETION DATE September 30, 2005

DATA REPORTING

PRODUCT CODES	PRODUCT/ASSIGNMENT CODES
Industry Code – 69, 70, 71 (See Data Codes Manual Product Code Section)	71004 (CGMP) 71004A (NON-CGMP) 71S004 (State Contract) 71004F (BSE Activities: FDA Licensed Feedmill) 71004G (BSE Activities: Non–FDA Licensed Feedmills, Protein Blender, Feed Distributors and Retailers) 71S007 (State Contract BSE Activities: FDA Licensed Feedmill) 71S008 (State Contract BSE Activities: Non-FDA Licensed Feedmills)

FIELD REPORTING REQUIREMENTS

1. Hard Copy Reporting

When a District becomes aware of any significant adverse information which 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 (kbell@cvm.fda.gov) or FAX (301-594-1812). HFV-230, in turn, will convey the information to other interested CVM units.

Send copies of the EIR sheets for those Out-of-Business (OOB) or Not Official Establishment Inventory (NOEI) firms to HFV-226 as directed by Field Management Directive (FMD) #92. Also send a copy of the cover sheet(s) to HFD-095 for cancellation of Drug Registration.

Forward Attachment D 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 the Bovine Spongiform Encephalopathy (BSE) inspections under the following PAC codes:

71003F - BSE Activities (FDA Feed Contaminants Program) (Renderers)
71004F - BSE Activities: Licensed Feedmills (Feed Manufacturing Compliance Program)
71004G -BSE Activities: Non-FDA Licensed Feedmills, Protein Blenders, Feed Distributors and Retailers (Feed Manufacturing Compliance Program)
71006F - BSE Activities (Illegal Residues in Meat & Poultry Program)(Producers)
71S007 - BSE Activities (State Contract inspection for BSE activities at FDA Licensed Feedmills)
71S008 - BSE Activities (State Contract inspection for BSE activities at Non-FDA Licensed Feedmills)
71S009 - BSE Illegal Tissue Residue State Contract Inspections

If multiple items are covered during the inspection, be sure to report the portion of time spent on this assignment separately.

A copy of the completed BSE **(Attachment B)** checklist should be forwarded to CVM, Division of Compliance, Compliance Information Management Team, HFV-235, as soon as possible, but no later than ten (10) days after completion of the inspection.

Not all reporting are made to CVM with in 10 days after the completion of the inspection. States that do contract work have thirty (30) days to submit their inspectional paper work to FDA.

PART I - BACKGROUND

OVERVIEW

This Compliance Program, in the past, had been limited to medicated feed manufacturing. We have, however, revised the title of the program to **Feed Manufacturing Compliance Program** since work under this program covers now both non-medicated and medicated feed manufacturing. This change was in response to the growing concern over the safety of feed ingredients and their public health impact.

The term "animal feed" is defined in Chapter II 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 21 CFR 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, 21 Code of Federal Regulations (CFR) Part 515, governing medicated feed mill licenses published November 19, 1999.

Any new animal drug approved for use in animal feed is placed in one of two categories, Category I or II. 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.

CVM will be issuing regulations clarifying the manufacture of free choice feeds and the manufacture of liquid Type B feeds where the formula or specifications are not published in 21 CFR Part 558, New Animal Drugs for Use in Animal Feeds.

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 December 8, 2000, and are found in 21 CFR 558.6. To date only one VFD drug has been approved, **Tilmicosin**, 21 CFR 558.618.

We have particular concern with the use of mammalian protein in feed for ruminants because of the possible transmission of the causative agent for Bovine Spongiform Encephalopathy (BSE). BSE is a fatal animal disease that may be linked to a fatal human disease called new variant Creutzfeldt-Jakob Disease (vCJD). To help prevent the establishment and amplification of BSE in the U.S., FDA published regulations prohibiting the use of certain mammalian protein in feed for ruminant animals. These regulations (21 CFR 589.2000) became effective August 4, 1997. Inspection of feed manufacturing facilities to determine their compliance with the new regulation is a high Agency priority.

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 as a model to generate actual feed labels by manufacturers

Bovine Spongiform Encephalopathy (BSE):

A transmissible, slowly progressive degenerative disease of the central nervous system of cattle. Its clinical signs include abnormal behaviors usually beginning with apprehension, increased reaction to sound and touch, a swaying gait, and sometimes high stepping. This disease has a prolonged incubation period and, once signs appear, is fatal. It has been called "mad cow disease."

Carryover:

Cross-contamination of feeds during manufacture with low levels of drugs or ruminant feeds with prohibited protein material derived from mammalian tissue.

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 require a withdrawal period at the lowest continuous feeding level in at least one animal species for which the drug is approved or drugs 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 is 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., 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 or prohibited mammalian protein product material that may be remaining in the equipment.

Free-choice:
Administration of animal drugs which 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 tank, 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.

Prohibited Protein Derived from Mammalian Tissues:
Any protein-containing portion of mammalian animals excluding blood and blood products, gelatin, inspected meat products which have been cooked and offered for human food and further heat processed for feed (such as plate waste and used cellulosic food casings), milk products (milk and milk proteins), and any other product whose only mammalian protein consists entirely of porcine or equine protein. This material is prohibited from use in ruminant feed.

Protein Blender:

Firms or individuals that obtain processed animal proteins from more than one source or from more than one species, and subsequently mix (blend) or redistribute an animal protein product.

Renderer:

Firms or individuals that process slaughter by-products, animals unfit for human consumption, or meat scraps into animal protein products such as meat and bonemeal.

Ruminants:

Includes any member of the order of animals which has a stomach with four chambers (rumen, reticulum, omasum, and abomasum) through which feed passes in digestion. The order includes, but is not limited to cattle, buffalo, sheep, goats, deer, elk, and antelopes.

Ruminant Feeder:

Establishments and individuals that care and feed ruminant animals. This can include a dairy, a feedlot, a veal raising operation, and others.

Transmissible Spongiform Encephalopathies (TSEs):

TSEs are progressively degenerative central nervous system diseases of humans and a number of animal species, primarily ruminants, characterized by a long incubation period, a short clinical course and a 100% death rate. Animal TSEs include sheep scrapie, Bovine Spongiform Encephalopathy (BSE), transmissible mink encephalopathy, feline spongiform encephalopathy, and chronic wasting disease of deer and elk. TSEs in humans include Creutzfeldt-Jakob Disease (CJD), new variant CJD, Gerstman-Straussler-Scheinker syndrome, kuru and fatal familial insomnia.

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 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, 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, licensed feed mill must manufacture the feed.

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 from 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. 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. 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 must notify FDA/CVM of their intent to distribute at the following address:

Center for Veterinary Medicine
HFV-226
7500 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

This Compliance Program has, in the past, been limited to medicated feed manufacturing. We have, however, revised the title of the program to **Feed Manufacturing Compliance Program** to incorporate inspectional and regulatory coverage for both non-medicated and medicated feed manufacturing.

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 conduct inspections of firms (non-medicated feed mills, medicated feed mills, renderers, distributors, etc.) producing, using and feeding mammalian protein product(s) to ensure compliance with 21 CFR 589.2000.
- 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 utilizes 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,; the new animal drug regulations in 21 CFR Part 558; and/or the BSE feed regulation requirements in 21 CFR 589.2000. 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

1. BSE and For Cause (Priority 1)

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

2. Re-inspections (Priority 2)

Conduct re-inspections of a firm whose most recent inspection was classified Official Action Indicated (OAI) except for firms in the pre-approval mode. Re-inspection of the OAI firm should occur within 90 days of issuance of a Warning Letter to determine whether CGMP violations continue or have been corrected.

This priority also includes firms that were not in compliance with the BSE rule. Re-inspection of these facilities should be conducted within 90 days.

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 must determine the applicant's knowledge of the CGMP requirements and its preparedness to comply.

4. Biennial Inspections (Priority 4)

Conduct biennial CGMP inspections of licensed firms whose most recent CGMP inspection was classified No Action Indicated (NAI) or Voluntary Action Indicated (VAI). These inspections will also address BSE inspectional matters.

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. These inspections also include information collection for BSE inspections (Priority 1).

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 prohibited protein material has or may have been fed to ruminant animals or other serious deviations from compliance with 21 CFR 589.2000, (2) that there is a potential for causing unsafe drug residues in food animals, (3)

that health problems in animals fed the medicated feed have occurred or may occur, or, (4) 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, **Attachment A**) 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. 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, 301-827-6657, 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 one VFD drug, **Tilmicosin**, 21 CFR 558.618, is 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. Bovine Spongiform Encephalopathy (BSE)

Inspections should determine compliance with 21 CFR 589.2000. Firms manufacturing feeds containing mammalian proteins prohibited for use in ruminant feed must comply with these regulations. If investigators find the firm is not in compliance with 21 CFR 589.2000, investigators will spend time educating firm management of the requirements of 21 CFR 589.2000. Repeated or egregious violations should be documented for possible enforcement action. See **Attachment B**.

F. Registration Cancellation and Medicated Feed Mill License Voluntary Withdrawal

Provide the form letter (**Attachment D**) 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.

G. 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.

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 must 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 manufacturing to determine if they are in compliance with the CGMP requirements and inspectional and regulatory coverage of both medicated and non-medicated feed manufacturing for compliance with BSE feed regulation requirements.

Coverage will be provided during inspection to address compliance with the BSE feed regulations. See **Attachment B**.

Firms planning to manufacture medicated feeds that require a medicated feed mill license must comply with the requirement 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. 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 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 (**Attachment A**) as a guide to recording observations and evaluating CGMP compliance.

EACH "NO" ANSWER ON THE FORM FDA 2481 MUST 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 Inspector's Operation 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 must 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 must 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 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 (**Attachment A**) 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, 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, a, b, c, and d, 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 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 item 52 and 55,** deal with these requirements.

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. 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, and any circumstances/assays which 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.

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. Many firms believe the burden is upon the FDA to prove that unsafe products have been manufactured. If the FDA wanted to take a civil or criminal legal action, or an administrative action, it would have to prove its case. However this does not have anything to do with the firm's responsibility to prove that its procedures and practices are effective. This is an underlying concept of CGMPs. If the adequacy of the firm's clean-out procedures are questioned, follow 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 or prohibited mammalian protein product material that may be remaining in the equipment. 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 Compliance Policy Guide 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, this procedure raises other feed and environmental safety questions and normally should not be 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 must 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 develop 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. When determining if the firm fails to meet specifications, consider the firm's investigation and evaluation while focusing on the significance of the complaint.

2. Bovine Spongiform Encephalopathy (BSE)

If this is the initial inspection of a firm for compliance with 21 CFR 589.2000, determine if the firm has a copy of this regulation and the appropriate Small Entities Compliance Guide and note its response on the checklist. There are four (4) Small Entities Compliance Guides, one each for 1) renderers, 2) protein blenders, feed manufacturers and distributors, 3) feeders of ruminant animals with on-farm mixing operations and 4) feeders of ruminant animals without on-farm mixing operations. If the firm does not have a copy, provide copies of it to firm management. In all cases discuss with the firm what is a prohibited material under the regulations and their responsibilities. The guides you will most likely use for inspections done under this program are Guidance for Industry #68, and #70. Copies can be found on CVM Homepage.

See **Attachment F** for a suggested approach and guidance for conducting an inspection for compliance with 21 CFR 589.2000.

3. **Electronic Records and Signatures - 21 CFR Part 11,**

There has been a lot of concern about 21 CFR Part 11 by both the feed industry and by FDA Field personnel. Specifically, both have stated various opinions as to the applicability of the electronic signature and recordkeeping requirements to the feed mill industry. To clarify, the Part 11 regulations apply to all FDA program areas.

The Food and Drug Administration issued guidance on the implementation of Part 11 (see CPG 160.850) on May 13, 1999. The guidance clearly states that Part 11

- does not mandate electronic recordkeeping
- applies to those records required by an FDA predicate rule
- applies to signatures required by an FDA predicate rule
- applies to signatures that are not required, but appear in required records

Part 11 also describes the technical and procedural requirements that must be met if a person chooses to maintain records electronically and use electronic signatures.

CVM has concluded it is not appropriate to use inspectional discretion on whether or not to apply Part 11 requirements for CGMP inspections of the medicated feed industry. To do so would be inconsistent with agency policy for regulated industries and will in essence establish a non-uniform application of agency regulations. Regulatory significance and subsequent actions, if any, will be evaluated on a case-by-case basis. In fact, the Part 11 guidance document states that when persons (firms) are not fully compliant with Part 11, decisions on whether or not to pursue regulatory actions will be based upon and may include the following:

- Nature and extent of Part 11 deviation(s)
- Effect on product quality and data integrity
- Adequacy and timeliness of planned corrective measures
- Compliance history of the establishment, especially with respect to data integrity

FDA will consider regulatory action with respect to Part 11 when the electronic records or electronic signatures are unacceptable substitutes for paper records or handwritten signatures, and therefore, requirements of the applicable regulations (e.g., CGMP regulations) have not been met. CVM officials, in conjunction with medicated feed program personnel and field investigators will evaluate on a case-by-case basis whether regulatory action is required.

Significant violations to the recordkeeping requirements are reportable observations and should be recorded and documented as would any other CGMP violation.

4. 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.

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 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 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.

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

5. **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 Act and FDA jurisdiction. At a minimum, a documentary sample should be collected for any violative **asterisked** item on the 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 above 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.

6. **General Sampling Precautions/Additional Information**

See Investigations Operations Manual (IOM) Sampling Schedule Chart 16 for sample sizes, etc., for potency and drug carry-over determinations in feed.

- 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.

7. **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 5 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 expeditiously correct violative conditions. 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 promptly notified 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

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 E** 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. In accordance with the delegation of authority, 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), (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 Articles.
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.

* ***Items "a, b and d"*** require Center concurrence prior to issuance of a Warning Letter. (See Chapter 4 of the FDA Regulatory Procedures Manual) ***Violations of item "e" should be forward to the Center for consideration of appropriate enforcement.***

3. **Violations of the BSE Feed Regulation**

What do you do if this firm is not complying with the regulation?

- Issue a FDA 483 or equivalent state document.
- Discuss the non-compliance areas with management.
- Be sure to leave a copy of the Small Entities Compliance Guide and any other educational materials.
- Distribution of product containing prohibited material without the required caution statement should be documented for consideration of a Warning Letter.
- Failure to provide measures to prevent commingling and cross contamination of prohibited from non-prohibited material should be documented for consideration of a Warning Letter.
- Refer to update BSE Enforcement Strategy for further guidance.

4. **Violative Surveillance Sample**

   If sizeable quantities of the violative medicated or BSE 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.

5. **Import**

   Detain or refuse entry of medicated feeds, which appear to be in violation of the 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 - Inspection
2. 21 CFR Part 225, Current Good Manufacturing Practice Regulations for Medicated Feeds
3. 21 CFR Part 558, New Animal Drugs for Use in Animal Feeds
4. 21 CFR Part 515, Medicated Feed Mill License
5. 21 CFR Part 558.6, Veterinary Feed Directive
6. 21 CFR Part 11, Electronic Records; Electronic Signatures
7. Official Publication 2001, Association of American Feed Control Officials, Inc
8. Official Methods of Analysis of the Association of Official Analytical Chemists, 17th ed., 2000
9. CPG 615.100, Extra-Label Use of New Animal Drugs in Food-Producing Animals
10. CPG 615.200, Proper Drug Use and Residue Avoidance by Non-Veterinarians
11. CPG 660.100, Failure to Register
12. CPG 680.200, CGMP Regulations for Medicated Feeds--Daily Inventory Requirements
13. CPG 680.500, Unsafe Contamination of Animal Feed from Drug Carryover
14. CPG 680.600, Sequencing as a Means to Prevent Unsafe Drug Contaminants in the Production, Storage, and Distribution of Feeds
15. CPG 666.100, Alternate Feeding of Different Medicated Feeds
16. CPG 689.100, Direct-Fed Microbial Products
17. CPG 160.100, Regulatory Actions and Small Business
18. CPG 7155a.19, MOU with USDA, Food Safety and Inspection Service and Agricultural Marketing Service and EPA
19. Trade Guides such as Feed Additive Compendium, The Miller Publishing Co., Minneapolis, MN.
20. Animal Drug Availability Act of 1996
21. FDA/CVM Guidance for Industry documents on BSE are located on CVM's Internet Web Site at: http://www.fda.gov/cvm
22. FDA/CVM Guidance on Veterinary Feed Directive, #120
23. Guidance For Industry: GMP'S For Medicated Feed Manufacturers Not Required to Register and Be Licensed with FDA
24. Regulatory Procedures Manual

B. ATTACHMENTS

Attachment A - Inspection Report Form FDA 2481
Attachment B - BSE Information, Report of Inspection for Compliance with 21 CFR 589.2000
Attachment C - Drug Category List (I and II)

Attachment D - Sample Form Letter to Voluntarily Withdraw Approval of Medicated Feed Mill License
Attachment E - Model Warning Letter
Attachment F – Inspectioanl Guidance – For Compliance with 21 CFR 589.2000 for Feed Manufacturers, Protein Blenders, Distributors

C. PROGRAM CONTACTS

1. ORA Contacts

- FDA personnel will direct inspectional inquiries to the Division of Emergency and Investigational Operations/Drug Group, HFC-130, on 301-443-1240.
- James Dunnie on 301-827-5652.
- 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

a. Program and Administrative Inquiries
Patsy Gardner, Program Monitor
Division of Animal Feeds
Medicated Feeds Team, HFV-226
E-Mail Address: PGardner@CVM.FDA.GOV
Phone: 301-827-0187

b. Regulatory Inquiries
Kim Bell
Division of Compliance
Drugs and Device Team, HFV-232
E-Mail Address: KBell@CVM.FDA.GOV
Phone: 301-827-0178

c. Program Manager
Jo Gulley, Team Leader
Medicated Feeds Team, HFV-226
Division of Animal Feeds
E-Mail Address: jgulley@CVM.FDA.GOV
Phone: 301-827-0170

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

MEDICATED FEEDS INSPECTION REPORT

DATE OF INSPECTION	
NAME OF INSPECTORS	
FIRM NAME ADDRESS ZIP CODE COUNTY	

SUMMARY OF FINDINGS

(Summarize the inspection factually and objectively from observations of the condition and practices of the firm)

HISTORY OF BUSINESS

1. PARENT FIRM, if applicable (NAME/ ADDRESS):	2. CORPORATE OFFICERS (Name, title, business address):

3. FDA REGISTRATION/LICENSE STATUS: (Check appropriate status)	4. TYPE OF FIRM: (Check appropriate type)	5. FEED PREPARED FOR: (Check all that apply)
☐ a. Unknown	☐ a. Commercial Feed Mill	☐ a. Beef Cattle ☐ e. Poultry
☐ b. Non-registered	☐ b. Custom Formula Mixer	☐ b. Dairy Cattle ☐ f. Fish
☐ c. Registered Registration number:_____	☐ c. Mixer-Feeder	☐ c. Swine ☐ g. Other (Exotic/ Species) _____
☐ d. Licensed License number:_____	☐ d. Other: Please specify: _____	☐ d. Sheep/Goats

6. Volume of business:		7. Interstate business:	
	a. Annual tonnage of all MEDICATED feeds manufactured.	Y/N:	a. Interstate business received?
	b. Annual tonnage of all Non-MEDICATED feeds manufactured.	Y/N:	b. Interstate business sold? If yes, percentage sold? _____%

RESPONSIBLE PERSONNEL

8. Name and title of most responsible individual at this plant to receive copy of report. (If more than one person, list.)	9. Indicate to whom FDA forms were issued, if more than one person, list all.

NOTES: The key CGMP elements are designated on this form with asterisk (**).
Items not covered on this form should be marked with N/C.

Each of the following questions shall be answered. Each "NO" answer shall be explained in the narrative block. Precede any explanation with appropriate item/question number.

VETERINARY FEED DIRECTIVE (VFD) DRUGS / FEEDS

Y/N	10. Does firm manufacture feeds containing VFD drugs? If the answer is yes, continue with question 11-15. If the answer is no, skip to item number 16.	NARRATIVE
Y/N	11.Does the firm distributes VFD feeds to other distributors or manufacturers?	
Y/N	12. Has the firm supplied to CVM a written letter of intent to distribute VFD Feeds?	
Y/N	13. Are copies of letters of acknowledgement maintained on file at this firm?	
14. State the number of VFD orders reviewed during inspection: _____		

VETERINARY FEED DIRECTIVE (VFD) DRUGS / FEEDS, continued:

Note: If the response to is "yes" to any part of item 14, but errors were found in what was observed/provided, please describe and elaborate in the narrative section below. Additionally, report in the narrative if firms are found to be operating outside of the VFD approval; for instance, is there evidence that there are other products being used, promoted or handled as VFD drugs? If more than 3 VFD orders are examined, please record findings using additional narrative page(s) or sheets of paper.

15. For the VFD orders reviewed (e.g., up to three in number), did they contain the following information:	VFD order #1		VFD order #2		VFD order #3	
a. The name, address and telephone number for the veterinarian and client.	Y	N	Y	N	Y	N
b. Identification of the animals to be treated, including the identification of the species, number of animals, and the specific location of the animals.	Y	N	Y	N	Y	N
c. Date of treatment and, if different, date of prescribing the VFD drug.	Y	N	Y	N	Y	N
d. Name of the animal drug.	Y	N	Y	N	Y	N
e. Level of animal drug in the feed and the amount of feed.	Y	N	Y	N	Y	N
f. Feeding instructions with withdrawal time.	Y	N	Y	N	Y	N
g. Expiration date of the VFD.	Y	N	Y	N	Y	N
h. Any special instructions necessary for use of the drug in conformance with the approval.	Y	N	Y	N	Y	N
i. Required cautionary statements.	Y	N	Y	N	Y	N
j. Number of refills, if permitted by the approval.	Y	N	Y	N	Y	N
k. Signature of the veterinarian.	Y	N	Y	N	Y	N
l. The veterinarian's license number and the name of the State issuing the license.	Y	N	Y	N	Y	N
m. Other information as required by the individual drug approval.	Y	N	Y	N	Y	N

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		NARRATIVE:
PERSONNEL (21 CFR 225.10)		
Y/N	16. Do the employees involved in the manufacture of medicated feed understand the manufacturing or control functions they perform, including the proper use and location of the equipment? For either response (i.e., "yes" or "no"), **elaborate** in the narrative section.	
Y/N	17. Are the employees provided with on-going evaluation and supervision? If yes, include how assessed.	
BUILDINGS (21 CFR 225.20)		
Y/N:	18. Are the grounds of the facility adequately drained and maintained?	
19. In regards to the buildings:		
Y/N:	a. Are they clean, orderly and suitably constructed?	
Y/N:	b. Are the control practices for rodents, birds, insects, and other pests effective?	
Y/N:	c. Do they have facilities to promote personal hygiene?	
20. Do the buildings provide adequate space for:		
Y/N	a. Receipt, inspection, storage, and processing of components?	
Y/N	b. Manufacturing, packaging, and labeling of medicated feeds?	
Y/N	c. Storage of containers, packaging materials, labeling, and products?	
Y/N	d. Routine maintenance of equipment?	
EQUIPMENT (21 CFR 225.30)		
21. Describe equipment used for mixing/blending of feeds in the narrative.		
22. With regards to assuring the uniformity of medicated feeds:		
Y/N	a. When installed, was/were the mixer(s)/blender(s) evaluated for their ability to produce feeds of uniform quality?	
Y/N	b. Since installation, has the firm determined that the mixer's ability to produce a uniformly mixed feed has not changed? Explain.	
Y/N	23. Has all production equipment, particularly those that are automated and/or computerized, been properly installed and verified to be able to reliably perform as intended?	

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		NARRATIVE:
EQUIPMENT (21 CFR 225.30)		
Y/N:	24. Whether manually or by automated means, are drugs accurately weighed?	
Y/N:	**25. Are ALL scales and metering devices tested for accuracy upon installation and at least once per year thereafter?	
Y/N:	26. Is equipment constructed to allow inspection and use of clean-out procedures?	
Y/N	27. Is all equipment reasonably clean and properly maintained?	
Y/N	28. Is all equipment constructed to prevent contamination with lubricants, coolants, etc.?	
Y/N:	29. Is all equipment of suitable size, design, construction, and precision for the intended purpose?	
USE OF WORK AND STORAGE AREAS FOR OTHER PURPOSE (21 CFR 225.35)		
Y/N:	**30. Does the firm avoid storage or handling of toxic or unapproved feed additives (i.e., fertilizers, herbicides, insecticides, rodenticides and pesticides not approved for use in feed) in the same equipment or areas as medicated feeds?	
EQUIPMENT CLEANOUT (21 CFR 225.65)		
Y/N:	31. Do clean out procedures exist for all equipment used in the manufacture and distribution of medicated feeds? If procedures exist, **specify the methods**, for example: physical, flushing, sequencing, etc.	
Y/N:	**32. Does the clean out procedure appear adequate to prevent unsafe contamination? **If no, explain.**	
Y/N:	33. Is there documentation that equipment clean out procedures are actually being performed?	
Y/N:	34. Describe disposition of clean out material.	

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CONTROL OPERATIONS	
Y/N	35. Are feeds stored in a manner to prevent mixups with other feeds?
Y/N	36. Is the method of dust control adequate to minimize potential contamination?
37. Is there adequate disposition of:	
Y/N	a. Spillage?
Y/N	b. Leaks?
Y/N	c. Broken Bags?
Y/N	d. Floor sweepings?
Y/N	e. Returns?
Y/N:	38. Are drugs used in accordance with their labeled directions, including appropriate species, drug levels, and use.
DRUG COMPONENTS (21 CFR 225.42)	
39. Report "**DRUGS COMPONENTS ON HAND**" in self-titled section of this report (page 13).	
Y/N:	**40. Are drugs properly identified, handled and controlled to maintain their integrity and identity?
Y/N:	41. Are drugs properly stored? (e.g., Are drugs labeled "Store in a cool, dry place", or "Store between 32° -81° F", so stored?)
Y/N:	42. Are all drugs within their expiration date?
Y/N:	43. Are there **RECEIPT RECORDS** for incoming lots of drugs? If yes, answer item 44 a-f below.
44. Do the **Receipt Records** show for each lot of drugs:	
Y/N	a. Identity and Quantity?
Y/N	b. Name of supplier?
Y/N	c. Supplier's lot number or number assigned by the manufacturer
Y/N	d. Date received?
Y/N	e. Condition of drug received?
Y/N	f. Return of damaged goods?
Y/N:	**45. Is there a **DAILY INVENTORY RECORD** for each lot of drug (separate from the production record)?

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DRUG COMPONENTS (21 CFR 225.42), continued	
46. Do the Daily Inventory Records for each drug:	
Y/N	a. Quantity of drug on hand at beginning and end of the work day?
Y/N	b. The amount of each drug used, sold or otherwise disposed of?
Y/N	c. The batches or production runs of medicated feed in which each drug was used?
Y/N	d. Actions taken to reconcile any discrepancies in the daily inventory record?
47. Does the firm's **DRUG INVENTORY system:	
Y/N:	a. Make a daily comparison between actual amount of drug used and theoretical drug usage?
Y/N	b. Have drug inventory records that agree with calculated usage?
Y/N:	c. Include a working definition of what it considers as constituting a significant discrepancy in its drug inventory?
Y/N:	d. Include procedures for holding feeds on the premises until a significant discrepancy is reconciled?
Y/N:	48. Are there any documented significant discrepancies in the firm's drug inventories? If yes, answer a-b below; If not, skip to item 49.
Y/N:	a. were documented discrepancies investigated?
Y/N:	b. were corrective action taken?
Y/N:	49. Do the firm's current drug inventories agree with the amount of drug currently on hand?
Y/N:	50. Are all required drug records kept on the premises for at least one year after complete use of a specific lot of drug component?
LABORATORY CONTROLS (21 CFR 225.58)	
Y/N:	**51. Are assays performed on all medicated feeds/manufactured according to the schedule specified in CFR 225.58?
Y/N:	**52. Are investigations performed and appropriate corrective actions taken in response to "out of limits" assay reports?
Y/N:	53. Are all investigations documented in writing?
Y/N:	54. Are results of assays kept on the premises for not less than one year after distribution of that feed?
Y/N	**55. When Category I drugs are assayed and found to be out of limits, are investigations performed?
Y/N:	56. Are reports made to CVM of confirmed "out of limits" assays of medicated feeds that have been distributed?

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		NARRATIVE:
LABORATORY CONTROLS (21 CFR 225.58)		
57. Provide the following information on any confirmed "out of limits" results: a. Name of feed(s) and drug(s). b. Production date or code c. Drug guarantee and assay result.		
LABELING (21 CFR 225.80)		
Y/N:	58. Does the accompanying labeling (including invoices if used as labeling) include drug level, directions for use and any required withdrawal or warning statements for safe, effective use of the medicated feed?	
Y/N:	59. Upon receipt from either an outside printer or in-house print shop, are labels and labeling (including placards and pre-printed bags) proofread against the MASTER RECORD FILE to verify their suitability and accuracy?	
Y/N:	60. Is the proofread label/labeling/pre-printed bag initialed by a responsible individual, dated and kept one year after all labels from that batch have been used?	
Y/N:	**61. Are labels handled and stored in a manner to prevent mixups and periodically reviewed to discard discontinued labels?	
**62. Does the firm adequately label the following:		
Y/N:	a. Bagged feeds?	
Y/N	b. Bulk feeds?	
Y/N	c. Custom formula feeds?	
63. When the firm distributes medicated feed in bag or bulk:		
Y/N	a: does complete labeling accompany the shipment? (Note: ***The labeling may consist of a placard or other labels attached to the invoice or delivery ticket, or manufacturer's invoice that identifies the medicated feed and includes adequate information for the use of the medicated feed).***:	
/	b. Describe what procedures does the firm use for providing the consignee with labeling upon delivery in the narrative.	
MASTER RECORD FILE (21 CFR 225.102)		
Y/N:	64. Is there a Master Record File or its equivalent for each medicated feed?	

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MASTER RECORD FILE (21 CFR 225.102), continued:		NARRATIVE:
**65. Does the Master Record File contain the following for each medicated feed:		
Y/N:	a. Name of medicated feed?	
Y/N:	b. An accurate formula, including the appropriate levels of drugs and non-drug ingredients under 21 CFR 573 (Food Additives) and 21 CFR 582 (GRAS).	
Y/N:	c. A copy or description of the label or labeling that will accompany the medicated feeds.	
Y/N	d. A copy of NADA approved Blue Bird Labeling, or a reference to electronic access to such labeling.	
Y/N:	e. Manufacturing procedures including mixing steps, mixing times, assay requirements and the appropriate control directions?	
Y/N:	f. Procedures for estimating quantity produced for bulk feeds?	
Y/N:	66. Is each Master Record File prepared, checked and signed or initialed by a qualified person?	
67. If all or portions of the Master Record File are computerized and/or electronically transmitted from another location, what steps are in place to protect the integrity of the data and signatures? ***Describe in the narrative.***		
Y/N:	68. Is each MASTER RECORD FILE kept on the premises for one year after production of the last batch or production run to which it pertains?	
PRODUCTION RECORDS (21 CFR 225.102)		
Y/N:	69. Is there a production record prepared for each batch or production run of medicated feed produced?	
Y/N:	a. are the records are generated/maintained electronically?	
Y/N:	b. do those records include alarms or error messages that occurred during production and any actions taken to clear the error or override the operation of the computer?	

PRODUCTION RECORDS (21 CFR 225.102), continued:		NARRATIVE:
**70. Does the production record:		
Y/N:	a. provide a complete and traceable history of the production of a batch or production run?	
Y/N	b. Product identification?	
Y/N	c. Date of production?	
Y/N	d. Written endorsement by a responsible person?	
Y/N	e. Name and quantity of drug components used?	
Y/N	f. Theoretical quantity of medicated feed to be produced?	
Y/N	g. Actual quantity of medicated feed produced?	
Y/N:	71. Do production records identify specific equipment and bins used in that production if the firm has multiple pieces of the same equipment and multiple bins?	
Y/N:	72. Are steps in place to minimize mixups, such as running feeds into the wrong bins?	
Y/N:	73. Does the production formula agree with the formula in the MASTER RECORD FILE?	
PRODUCTION RECORDS (21 CFR 225.102), continued:		
Y/N:	74. Are production records checked by a responsible individual at the end of the working day to determine that all required production steps have been performed?	
75. Mixing: Provide in the narrative block the: a. Point in at which drug is added. b. Mixing time c. Manner in which mixing is timed.		
Y/N:	76. Has the firm defined what constitutes a significant discrepancy in production? (Including such aspects as theoretical vs. actual production yield, actual drug usage, etc.)	
Y/N:	77. Are significant discrepancies immediately investigated and do production records show the corrective actions taken?	
Y/N:	78. Is an individual batch or production run number, code, date or other suitable identification which permits tracing of the manufacturing history applied to the labeling of the medicated feed?	
79. Calculate drug levels in a representative number of feeds, and: a. State the number checked that were right. (In narrative) b. Report any discrepancies found. Provide evidence of the discrepancy, including formula.		
Y/N:	80. Is the original, copy, or electronic version of the production record kept on the premises for not less than one year from the date of production?	

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	DISTRIBUTION RECORDS (21 CFR 225.110)	NARRATIVE:
Y/N:	**81. Does each distribution record provide sufficient information, to relate complaints to specific batches or production runs?	
Y/N	82. Are distribution records kept on the premises for not less than one year after the date of shipment?	
	COMPLAINT FILES (21 CFR 225.115)	
Y/N:	83. Does the firm have procedures to use as follow-up in response to product complaints and reports of experiences of product defects?	
Y/N:	84. Is a file kept for each oral and written complaint or report of product defects? If, yes, does it contain:	
Y/N	a. Date of complaint?	
Y/N	b. Complainant's name and address?	
Y/N	c. Name and lot or number or date of manufacture of the medicated feed involved?	
Y/N	d. Specific details of the complaint?	
Y/N	e. Correspondence, including memoranda of conversations, from the complainant?	
Y/N	f. Description of all investigations?	
Y/N	g. Method of disposition of the complaint?	
Y/N:	85. Are reports of adverse experiences, drug mixups, and other failures of the drug to meet specifications reported as required to CVM?	

NARRATIVE:

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NARRATIVE:

DRUG COMPONENTS ON HAND			
TRADENAME	DISTRIBUTOR	DRUG	POTENCY

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DISCUSSION WITH MANAGEMENT

Describe in detail all recommendations and warnings given to management and their response to each deviation listed on the FDA 483.

REPORT OF INSPECTION FOR COMPLIANCE WITH 21 CFR 589.2000

Firm Name: _____ Date Inspected: _____

Firm Address: _____ Investigator: _____

Firm City/State: _____ District or State Agency: _____

CFN #: _____

❶ Type of firm inspected? (Check all that apply)

Renderer	☐	FDA Licensed Feed Mill	☐	Ruminant Feeder	☐
Protein Blender	☐	Non-FDA Licensed Commercial Feed Mill	☐	Hauler/Distributor	☐
On-farm Feed Mill	☐	Other: _____			

❷ This firm is already aware of 21 CFR 589.2000. YES ☐ NO ☐

Left a copy of the FDA "Guidance for Industry." YES ☐ NO ☐

❸ Do they receive products that contain or may contain prohibited material and subsequently use them in manufacturing or feeding? YES ☐ NO ☐

If this firm receives prohibited material for further distribution **only**, briefly describe this activity:

_____

❹ If the answer to #3 is "NO," list the sources of material and describe any safeguards the firm has in place to assure they do not receive prohibited material

_____

_____

_____

_____

For renderers, protein blenders, and feed manufacturers, if the answer to #3 above is "YES," complete questions #5 through #9 -

(If this is an inspection of a ruminant feeder, go to question #10)

❺ Are the products labeled with the caution statement "**Do not feed to cattle or other ruminants?**" YES ☐ NO ☐

❻ Does the firm maintain records sufficient to track the materials throughout their receipt, processing, and distribution including -

Date of receipt or purchase, or sale or delivery -	YES ☐ NO ☐
Name and address of the seller -	YES ☐ NO ☐
Name and address of the consignee -	YES ☐ NO ☐
Identification of the product -	YES ☐ NO ☐
Quantity -	YES ☐ NO ☐
Copies are available for inspection and copying -	YES ☐ NO ☐

❼ Is this firm processing or manufacturing and distributing both product containing prohibited material and product containing non-prohibited material? YES ☐ NO ☐

❽ If the answer to #7 is "YES," does the firm have a system in place to avoid commingling and cross contamination? YES ☐ NO ☐

Describe the separation system or clean-out process and any procedures to avoid commingling and cross contamination.

_____

_____

_____

❾ Does the firm have any safeguards in place to assure that outgoing product containing prohibited material is not shipped to ruminant feeders? YES ☐ NO ☐

Describe those safeguards?

_____

_____

_____

❿ Are ruminant feeders doing the following -

Observing the caution statement on feeds containing prohibited material YES ☐ NO ☐
Maintaining copies of labeling for feeds containing animal protein YES ☐ NO ☐
Maintaining copies of purchase invoices for feeds containing animal protein YES ☐ NO ☐

If you found any areas or items of non-compliance with 21CFR 589.2000, please list below -

_____

_____

_____

_____

Name and title of person interviewed: _____

Did the firm or individual make any commitments to correct their non-compliance? YES ☐ NO ☐

List those commitments -_____

_____

_____

_____

Are you attaching any further descriptions or any exhibits or records and/or labeling? YES ☐ NO ☐

Follow-up:
Needs additional educational material ☐
Reinspect to confirm corrections ☐ Target date for reinspection: _____
Recommend Warning Letter ☐
Other: _____

Distribution: 06-07-99

Category I			
Drug	**Assay Limits 1/ Type A**	**Type B Maximum (200 X)**	**Assay Limits 1/ Type B/C 2/**
Aklomide	90-110	22.75 g/lb (5.0%)	85-120
Amprolium with Ethopabate	94-114	22.75 g/lb (5.0%)	80-120
Bacitracin methylene disalicylate	85-115	25.0 g/lb (5.5%)	70-130
Bacitracin zinc	84-115	5.0 g/lb (1.1%)	70-130
Bambermycins	90-110	800 g/ton (0.09%)	80-120/70-130
Buquinolate	90-110	9.8 g/lb (2.2%)	80-120
Chlortetracycline	85-115	40.0 g/lb (8.8%)	80-115/70-130
Coumaphos	95-115	6.0 g/lb (1.3%)	80-120
Decoquinate	90-105	2.72 g/lb (0.6%)	80-120
Dichlorvos	100-115	33.0 g/lb (7.3%)	90-120/80-130
Diclazuril	90-110	182g/t (0.02%)	85-115/70-120
Efrotomycin	94-113	1.45 g/lb (0.32%)	80-120
Erythromycin (thiocyanate salt)	85-115	9.25 g/lb (2.04%)	<20 g/ton 70-115/150-50 >20 g/ton 75-125
Iodinated casein	85-115	20.0 g/lb (4.4%)	75-125
Laidlomycin	90-110	1 g/lb (0.22%)	90-115/85-115
Lasalocid	95-115	40.0 g/lb (8.8%)	Type B (cattle & sheep) 80-120 Type C (all) 75-125
Lincomycin	90-115	20.0 g/lb (4.4%)	80-130
Melengestrol acetate	90-110	10 g/ton (0.0011%)	70-120
Monensin	90-110	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

Category I			
Drug	**Assay Limits 1/ Type A**	**Type B Maximum (200 X)**	**Assay Limits 1/ Type B/C 2/**
			Liq. Feed: 80-120
Narasin	90-110	7.2g/lb. (1.6%)	85-115/75-125
Nequinate	95-112	1.83 g/lb (0.4%)	80-120
Niclosamide	85-120	225 g/lb (49.5%)	80-120
Nystatin	85-125	5.0 g/lb (1.1%)	75-125
Oleandomycin	85-120	1.125 g/lb (0.25%)	<11.25 g/ton 70-130 >11.25 g/ton 75-125
Oxytetracycline	90-120	20.0 g/lb (4.4%)	75-125/65-135
Penicillin	80-120	10.0 g/lb (2.2%)	65-135
Poloxalene	90-110	54.48 g/lb (12.0%)	Liq. Feed: 85-115
Ractopamine	85-105	1.8 g/lb (0.4%)	80-110
Salinomycin	95-115	6.0 g/lb (1.3%)	80-120
Semduramicin	90-110	2.25 g/lb (0.50%)	80-110
Tiamulin	100-108 90-115	113.4 g/lb 3.5 g/lb (0.8%) 5&10 g/lb	90-115 70-130
Tylosin	80-120	10.0 g/lb (2.2%)	75-125
Virginiamycin	85-115	10.0 g/lb (2.2%)	70-130
Zoalene	92-104	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 1/ Type B/C 2/**
Amprolium	94-114	11.35 g/lb (2.5%)	80-120
Apramycin	88-112	7.5 g/lb (1.65%)	80-120
Arsanilate Sodium	90-110	4.5 g/lb (1.0%)	85-115/75-125
Arsanilic acid	90-110	4.5 g/lb (1.0%)	85-115/75-125
Carbadox	90-110	2.5 g/lb (0.55%)	75-125
Carbarsone	93-102	17.0 g/lb (3.74%)	85-115
Clopidol	94-106	11.4 g/lb (2.5%)	90-115/80-120
Famphur	100-110	5.5 g/lb (1.21%)	90-115/80-120
Fenbendazole	93-113	8.87 g/lb (1.96%)	75-125
Halofuginone hydrobromide	90-115	272.0 g/ton (0.03%)	75-125
Hygromycin B	90-110	1200 g/ton (0.13%)	75-125
Ivermectin	90-105	1180 g/ton (0.13%)	80-110
Levamisole	85-120	113.5 g/lb (25%)	85-125
Maduramicin ammonium	90-110	545 g/ton (0.06%)	80-120
Morantel tartrate	90-110	66.0 g/lb (14.52%)	85-115
Neomycin Oxytetracycline	80-120 80-120	7.0 g/lb (1.54%) 10.0 g/lb (2.2%)	70-125 65-135
Neomycin Sulfate	80-120	100g/lb(22.0%)	70-125
Nicarbazin (powder)	98-106	5.675 g/lb (1.25%)	85-115/80-120
Nicarbazin (granular) Narasin	90-110 90-110	5.675 g/lb (1.25%) 5.675 g/lb (1.25%)	85-115/75-125 85-115/75-125
Nitarsone	90-110	8.5 g/lb (1.87%)	85-120
Nitromide, Sulfanitran, Roxarsone	90-110 85-115 90-110	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	85-115	17.5 g/lb (3.85%)	80-120

Category II			
Drug	**Assay limits 1/ Type A**	**Type B Maximum (100 X)**	**Assay Limits 1/ Type B/C 2/**
Pyrantel tartrate	90-110	36 g/lb (7.9%)	75-125
Robenidine	95-115	1.5 g/lb (0.33%)	80-120
Ronnel	85-115	27.2 g/lb (6.0%)	80-120
Roxarsone	90-110	2.275 g/lb (0.5%)	85-120
Roxarsone Aklomide	90-110 90-110	2.275 g/lb (0.5%) 11.35 g/lb (2.5%)	85-120 85-120
Roxarsone, Clopidol, Bacitracin methylene disalicylate	90-110 94-106 85-115	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	90-110 90-110	2.275 g/lb (0.5%) 5.5 g/lb (1.2%)	85-120 75-125
Sulfadimethoxine, Ormetoprim (5/3)	95-115 95-115	5.675 g/lb (1.25%) 3.405 g/lb (0.75%)	85-115/75-125 85-115
Sulfadimethoxine Ormetoprim (5/1)	95-115 95-115	85.1 g/lb (18.75%) 17.0 g/lb (3.75%)	85-115/75-125 85-115
Sulfaethoxypyridazine	95-105	50.0 g/lb (11.0%)	85-115
Sulfamerazine	85-115	18.6 g/lb (4.0%)	85-115
Sulfamethazine, Chlortetracyline, Penicillin	85-115 85-115 85-115	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, Chlortetracycline	85-115 85-115	10.0 g/lb (2.2%) 10.0 g/lb (2.2%)	80-120 85-125/70-130
Sulfamethazine, Tylosin	85-115 80-120	10.0 g/lb (2.2%) 10.0 g/lb (2.2%)	80-120 75-125
Sulfanitran, Aklomide	85-115 90-110	13.6 g/lb (3.0%) 11.2 g/lb (2.5%)	75-125 85-120
Sulfanitran, Aklomide, Roxarsone	85-115 90-110 90-110	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	85-115 90-110 90-110	13.6 g/lb(3.0%) 11.2 g/lb(2.5%) 2.27 g/lb(0.5%)	75-125 85-120 85-120

Category II			
Drug	**Assay limits 1/ Type A**	**Type B Maximum (100 X)**	**Assay Limits 1/ Type B/C 2/**
Sulfaquinoxaline	98-106	11.2 g/lb (2.5%)	85-115
Sulfathiazole, Chlortetracycline, Penicillin	85-115 85-115 80-120	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	94-106	45.4 g/lb (10.0%)	>7% 85-115; <7% 90-110
Tilmicosin	90-110	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 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)_____

Medicated Feed Mill License Number _____

_____
Firm Name

_____
Address

_____
City, State Zip

Sincerely Yours,

_____
Name and Title Date

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

RESPONSIBLE INDIVIDUAL, TITLE
FIRM NAME
FIRM MAILING ADDRESS

Dear _____:

An investigation 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 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

Inspectional Guidance - For compliance with 21 CFR 589.2000 for Feed Manufacturers, Protein Blenders, Distributors

BEFORE BEGINNING ANY INSPECTION, CHECK WITH YOUR FDA DISTRICT BSE MONITOR TO SEE IF THE FIRM HAS ALREADY BEEN INSPECTED.

I. Does the firm know about the new regulation?

If not, be sure and discuss the requirements of the regulation and leave a copy of the Small Entities Compliance Guide.

II. Does this firm receive and process prohibited material?

In obtaining an answer for this question, one approach is to simply ask, but be sure and include the following questions -

★What kind of protein products do they receive?
★Do they receive products with mammalian protein?
★If yes, what kind of mammalian protein?

A. If the answer to **II is NO,** they do not receive and process prohibited material, or **DO NOT KNOW**, do the following:

❶Do a walk through of the facility, especially looking at the receiving area and the ingredient storage area. Observe the material coming in and any material waiting to be processed. **DO YOU SEE ANY PROHIBITED MATERIAL OR ANY INGREDIENT LABELED WITH THE CAUTION STATEMENT REQUIRED BY 589.2000?**

❷Review a representative number [at least ten (10)] of receiving records and/or invoices for incoming material. DO THESE RECORDS INDICATE RECEIPT OF PROHIBITED MATERIAL?

If the answer here or to #1 is YES, copy the records and document for possible enforcement action.

❸Does this firm manufacture feed for ruminant animals? List all of the species for which animal feed is manufactured by this firm.

❹Determine what procedures or safeguards, if any, the firm has in place to assure they do not receive prohibited material. Describe those safeguards.

B. If the answer to **II is YES**, they do receive prohibited material, do the following:

❶Describe the type of prohibited material.

❷Do a walk through of the facility, especially looking at the receiving and storage area and observe the material coming in and any prohibited material in the ingredient storage area. Is the prohibited material identified?

❸Does this firm manufacture feed for ruminant animals? List all of the species for which animal feed is manufactured by this firm.

❹Review a representative number [at least ten (10)] of records of receipt for incoming prohibited material and for distribution of manufactured feed or feed ingredients containing prohibited material.
DO THEY CONTAIN THE REQUIRED INFORMATION?
If the answer is **NO**, copy the records and discuss the requirement with responsible management.
❺How do they label the feeds or feed ingredients containing prohibited material? Collect a representative copy of the label for each product containing prohibited material.
DO THEY BEAR THE REQUIRED CAUTION STATEMENT?
If the answer is NO, document for possible enforcement action.
❻Determine what procedures or safeguards, if any, the firm has in place to assure they do not distribute feed containing prohibited material to ruminant feeders. Describe those safeguards.
❼Make copies or record the information for incoming or outgoing products where the documents suggest possible violations, or otherwise as directed by CVM Assignment Reference #VA 8-BSE. This information may be used to select trace back and trace forward shipments of material for inspection for compliance with 21 CFR 598.2000.

C. Are they or do they plan to process and distribute both feeds or feed ingredients containing prohibited material and feeds and feed ingredients containing non-prohibited material?
❶If the answer is **YES**, they will process and distribute both, determine if they are or will be separating the receipt, processing, and storage of the products containing prohibited material from non-prohibited material.
❷Do a walk through of the incoming material receipt and storage, product processing and finished product storage areas. Describe the separation system and procedures to avoid commingling and cross contamination (dust control, separate equipment and/or buildings, other controls on incoming material and finished product identification and storage).
❸If they use the same equipment for both products, describe the clean-out procedures.
❹Does the firm maintain written procedures specifying clean-out and other procedures to separate prohibited material from non-prohibited material from the time of receipt until the time of shipment. If the answer is **YES, are they adequate**? If the answer is **NO to either question**, discuss this requirement with responsible management.
❺If the inspection reveals no controls in place to prevent commingling or cross contamination between product containing prohibited material and product containing non- prohibited material, document for possible enforcement action.

III. Reporting

1. Complete the checklist "REPORT OF INSPECTION FOR COMPLIANCE WITH 21 CFR 589.2000." **(Attachment B)**
2. Send one copy to each of the following -
   a) CVM, Division of Compliance, HFV-235,
      7500 Standish Place, Rockville, Maryland 20855
   b) BSE Monitor in the FDA District
3. Be sure to report time spent on this inspection under the PAC Code for BSE inspections of feed manufacturers and distributors, or protein blenders (71004G). If the inspection is covering multiple programs, report time spent on this part of the inspection separately.
4. Individual FDA district offices and states may have additional reporting requirements.