

CHAPTER 71 - Type A Medicated Articles

SUBJECT: Type A Medicated Articles		IMPLEMENTATION DATE: 08/05/2022
DATA REPORTING		
PRODUCT CODES	PRODUCT/ASSIGNMENT CODES	
Industry code: 67	71005 (GMP) 71005A (non-GMP)	

FIELD REPORTING REQUIREMENTS:

Advance Notification

The Center for Veterinary Medicine (CVM) encourages open communication regarding Compliance Program (CP) 7371.005 establishment inspections to mitigate risk, maximize resources and increase work efficiency. CP 7371.005 requires advance notification to FDA management during inspections when investigators reveal significant Current Good Manufacturing Practice (CGMP) deviations and safety risks that could result in a regulatory action (e.g., warning letter, seizure, and injunction) or a withhold recommendation for an application for a new animal drug. In these cases, advance notification should be given to CVM before the issuance of the Form FDA 483, Inspection Observations, while the inspection is still in progress. If any significant adverse conditions that could result in regulatory action (e.g., warning letter, seizure, and injunction) are observed, ORA’s Program Division should immediately inform CVM’s Division of Drug Compliance via CVMAntimalDrugGMP@fda.hhs.gov.

The ORA Division is responsible for completing the Establishment Inspection Report (EIR) with the initial inspection classification, within ORA’s established timeframes, consistent with [FMD 86: Establishment Inspection Report Conclusions and Decisions](#), FDA policies governing pharmaceutical quality, and this compliance program. The ORA Division files the inspection documents electronically using the specific module (eNSpect, or Compliance Management System (CMS)) accessible to both ORA and CVM.

If a firm is identified as Out-of-Business (OOB) or Not Official Establishment Inventory (NOEI), then via email, (1) notify the Compliance Program Manager at CVMAntimalDrugGMP@fda.hhs.gov and (2) alert CVMSurveillance@fda.hhs.gov for cancellation of the establishment animal drug registration.

eNSpect Reporting

Charge time spent covering the CVM regulated products against the Program/Assignment Code (PAC) listed below.

- A. Charge time for CGMP inspections to PAC 71005.
- B. Charge time for non-CGMP investigations or inspections to PAC 71005A.

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PART I – BACKGROUND

General

FDA (the Agency) regulates the manufacturing and distribution of drugs to assure compliance with the Federal Food, Drug, and Cosmetic Act (the Act), including section 501(a)(2)(B) of the Act, and the Code of Federal Regulations (CFR). The Food and Drug Administration Safety and Innovation Act (FDASIA), which amended the FD&C Act section 510(h), directs FDA to take a risk-based approach to inspecting both domestic and foreign drug manufacturing establishments. FDA has developed two basic strategies for inspections based on the FD&C Act, including Chapter 7 General Authority:

1. evaluating establishments through FDA CGMP inspections of the conditions/practices under which drugs are manufactured, packed, tested, and held, and
2. monitoring the quality of drugs through surveillance activities such as sampling, analysis, and evaluating products via agency programs (including evaluating foreign regulator inspectional findings conducted under mutual recognition agreements, complaints, field alert reports, adverse drug events and other drug experience reports).

CP 7371.005 Type A Medicated Articles provides guidance for implementing the strategies and explains risk-based inspectional requirements for drug manufacturing. Drugs are of an acceptable quality when manufacturing establishments are operating in a state of control. CP 7371.005 Type A Medicated Articles describes the agency’s inspectional strategy for monitoring manufacturing processes to ensure production of safe and effective drugs that are in compliance with CGMP, and requirements of New Animal Drug Applications (NADA), Abbreviated New Animal Drug Applications (ANADA), the Act and the CFR.

The inspectional guidance found in this program is structured to provide for efficient use of resources devoted to routine surveillance coverage, recognizing that in-depth coverage of all systems and processes is not feasible for all firms. Therefore, inspectional frequency and coverage is performed based on risk. This compliance program also provides for follow-up compliance coverage, as needed.

History

Type A medicated articles were originally regulated as “medicated premixes.” The medicated premix CGMP rule was published in 1967 [32 Fed. Reg. 15109 (Nov. 1, 1967)] and was recodified to Part 226 [40 Fed. Reg. 13996, 14031 (Mar. 27, 1975)] in 1975. In 1986, FDA published a rule restructuring the Agency’s medicated feeds program by creating a clear distinction between a new animal drug and an animal feed bearing or containing a new animal drug (i.e., a medicated feed). This rule established definitions for Type A medicated articles and Type B and C medicated feeds, and revised Part 226 to regulate “Type A medicated article(s)” instead of “medicated premixes.” [51 Fed. Reg. 7382, 7390 (Mar. 3, 1986)]. The applicable CGMP requirements were not changed, and the rule itself has only undergone minor substantive revisions since 1967.

Definitions

21 CFR Part 210.3 defines various terms used in FDA's CGMP regulations, and these definitions apply to Part 226.

In general, medicated feed is produced by taking a high potency article containing one or more drug substances (a "Type A medicated article", which often has potency similar to an Active Pharmaceutical Ingredient (API)) and diluting it with animal food ingredients to create a Type B (intermediate potency) or Type C (potency suitable for administration) medicated feed. The availability of drug in several standardized dilutions allows feed mills to produce medicated feed with less risk and with fewer CGMP controls than are needed at the Type A manufacturer, thus there are separate CGMP regulations for medicated feeds (21 CFR Part 225).

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 of another Type A medicated article or in the manufacturing of a medicated feed; the medicated feed can be either a Type B medicated feed or a Type C medicated feed. A Type A medicated article is the subject of an approved New Animal Drug Application (NADA), an Abbreviated New Animal Drug Application (ANADA), or an index listing on the Index of Legally Marketed Unapproved New Animal Drugs for Minor Species and is of a standardized potency. See 21 CFR 558.3(b)(2).

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% weight) and is intended solely for use in the manufacturing of other medicated feeds; the medicated feed can be 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 from an unstandardized drug component (bulk or "drum-run", which is a dried crude fermentation product). See 21 CFR 558.3(b)(3).

Type C: A Type C medicated feed is a feed that contains a new animal drug and 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 Type C medicated feed, or an unstandardized drug component with other ingredients to a level of use specified in an approved New Animal Drug Application under section 512(c) of the FD&C Act. See 21 CFR 558.3(b)(4).

Distinguishing Between Type A medicated articles and APIs: There is a high degree of similarity between APIs and Type A medicated articles, as both are highly concentrated sources of active ingredients that are used to manufacture drugs. The primary distinction between articles regulated as APIs vs. those regulated as Type A medicated articles is that APIs are not approved as stand-alone products, but Type A medicated articles have an approved NADA/ANADA that defines the article. Type A medicated articles have approved labeling which describes how the article can be used to further manufacture medicated feeds. In facilities which manufacture APIs and then produce Type A medicated articles from those APIs, investigators must take care to

distinguish which steps are considered API manufacturing (which is subject only to statutory CGMP, FD&C Act section 501(a)(2)(B)) and which steps are Type A manufacturing regulated under 21 CFR Part 226.¹ The approved application defines the Type A medicated article and can be used to distinguish the API manufacturing steps (e.g., those contained in a Drug or Veterinary Master File) from the Type A medicated article manufacturing steps.

RequirementsDrug Registration

Establishments manufacturing Type A medicated articles are required to [register](#) annually as drug establishments and are subject to inspection on a risk-based schedule under section 510 of the FD&C Act.

¹ For inspectional guidance regarding API manufacturing, see Compliance Program 7371.001 “Animal Drug Manufacturing Inspections”

PART II - IMPLEMENTATION

The purpose of this compliance program is to assure that a Type A medicated article(s) meets the requirements of the FD&C Act for safety, identity and strength and meets the quality and purity characteristic that it purports or is represented to possess.

Objectives

- To inspect establishments producing Type A medicated articles for compliance with 21 CFR Part 226 (Type A Medicated Article CGMP).
- To take regulatory action against adulterated and misbranded Type A medicated articles and violative firms.
- To identify firms in violation of CGMP that may result in the inability to approve pending applications for Type A medicated articles or withdraw approval of existing applications.
- To determine the distributors of Type A medicated articles and investigate whether they, their consignees, or the final users have proper authority to handle these products.

Program Management/Planning Instructions

Inspection Priorities

CVM uses risk-based criteria for inspection of Type A medicated article facilities. Within each work planning cycle, CVM will identify two tiers of domestic firms for surveillance inspection and will transmit this list to ORA. Tier 1 firms represent the highest priority for surveillance inspection. Tier 2 firms are lower priority for surveillance coverage. CVM will identify and notify ORA of the foreign firms for surveillance coverage.

Program Interactions

The Comprehensive Animal Food Inspection Compliance Program (CP 7371.000) and this compliance program are interrelated because many establishments will be producing both products. Medicated feeds inspections are conducted under a Federal/State program and subject to 21 CFR Part 225, while Type A medicated articles are inspected strictly under a federal program and subject to 21 CFR Part 226. This program is also related to the NADA/ANADA Pre-Approval Inspections (CP 7368.001) program and Animal Drug Manufacturing (CP 7371.001).

PART III - INSPECTIONAL

Surveillance Inspections

Surveillance inspections are inspections conducted as a routine assignment with no other indicators of non-compliance. Routine surveillance inspections of regulated facilities are used to monitor ongoing compliance with CGMP and other requirements.

Compliance Inspections

Compliance inspections are performed 1) to evaluate or verify compliance corrective actions after a regulatory action has been taken or 2) to evaluate a potentially violative situation of which FDA has become aware. The coverage in compliance inspections should focus on the preexisting or suspected violations and then expand accordingly to develop their scope and significance.

Compliance inspections must be thorough enough to allow FDA to make a determination regarding the overall compliance status of the establishment after any corrective actions are taken.

Compliance inspections include “for-cause” inspections, which are performed to investigate a specific problem that has come to the Agency’s attention. FDA may become aware of a problem via Field Alert Reports (FARs), industry complaints, recalls of adulterated or misbranded products, or by other means. These issues may be covered under other compliance programs or by a limited assignment memorandum.

State of Control

A drug establishment is operating in a state of control when its conditions and practices maintain compliance with the Act, including section 501(a)(2)(B) of the Act and portions of the CGMP regulations that pertain to their systems. An establishment in a state of control produces drugs for which there is an adequate level of assurance of quality, strength, identity, and purity.

Inspection Planning and Product Coverage

This Compliance Program is outlined to mirror the 5 Subparts of 21 CFR 226, which should guide the inspectional approach. While 21 CFR 226 is not outlined specifically into six systems, ORA’s systems-based inspectional approach is compatible. Note: Inspections of Type A medicated articles are not divided into full or abbreviated inspection options. (See [Surveillance Inspection Frequency / Depth](#))

The establishment inspection should cover at least one Type A medicated article. The basic approach is to determine whether the firm is complying with application commitments and CGMP. If the firm is in operation, investigators should personally observe the various manufacturing operations being performed.

When identifying products to cover and following up on potential deviations, investigators should apply a risk based inspectional approach. In general, the two most significant hazards that can be caused by Type A medicated articles are:

- Hazard: *Potential drug residues in animal tissue* (i.e., drug remaining in animal products consumed by humans). Some animal drugs are hazardous to humans when they exceed established tolerance levels.
 - Risk: FDA assesses the risk posed by residues when it approves a Type A medicated article and puts the article into one of two categories:
 - “Category II,” Type A medicated articles are used to manufacture medicated feeds that require a withdrawal period (i.e., period of time the animal must be held before slaughter) at the lowest use level for at least one major species² for which they are approved or are regulated on a “no-residue” basis or with a zero tolerance because of carcinogenic concern regardless of whether a withdrawal period is required in any species. Therefore, Category II articles are considered high risk. Any CGMP deficiency which could expose animals to higher amounts of a Category II drug than expected could cause a violative drug residue and a hazard to humans. [21 CFR 558.3(b)(1)(i)]
 - “Category I,” Type A medicated articles are used to manufacture medicated feeds that require no withdrawal period at the lowest use level in each major species for which they are approved or are approved for use only in minor species.³ [21 CFR 558.3(b)(1)(i)]. This means the Category I Type A medicated articles are relatively lower risk for causing a harmful residue.
 - A chart classifying all Type A medicated articles into Category I or II can be found at 21 CFR 558.4.
 - Potential Root Causes: Type A medicated article manufacturing issues that are most likely to lead to drug residues are improper mixing (resulting in some portions of a batch of Type A medicated article being super-potent), mislabeling/mix-ups of Type A medicated articles or their components, or contamination of the Type A medicated article with other APIs (e.g., due to improper cleaning of manufacturing equipment)
 - Inspectional Recommendations: Due to the higher risk, prioritize coverage of Category II drugs over Category I drugs. Within Category II drugs, CGMP

² Major species are dogs, cats, horses, pigs, cattle, turkeys, and chickens. Section 201(nn) of the FD&C Act ((21 U.S.C. § 321(nn)).

³ The term “minor species” means animals other than humans that are not major species. Section 201(oo) of the FD&C Act (21 U.S.C. § 321(oo)).

deviations that could cause a tissue residue are of greater concern (e.g., super-potency).

- Hazard: *Toxicity to other animal species*. Some drugs used in certain species are highly toxic to others. Individual deaths and even mass-fatality events can occur if animals are exposed to the wrong drug.
 - Risk: Facilities producing multiple Type A medicated articles are higher risk. The risk is increased when common equipment and/or common manufacturing areas are used. Certain individual drugs have known, significant risks, which can be found on drug labels and in the individual regulations governing the use of each drug. See 21 CFR Part 558, Subpart B for all the relevant regulations. For example, monensin can be safely used in some species, but is extremely toxic to others. (See, e.g., 21 CFR 558.355(d)(6) and (8)(i) noting hazards to equines and guinea fowl)
 - Potential Root Causes: Type A medicated article manufacturing issues that are most likely to lead to toxicity events are mix-up/mislabeled of Type A medicated articles or their components or contamination of the Type A medicated article with other APIs (e.g., due to improper cleaning of manufacturing equipment).
 - Inspectional Recommendations: Enhanced focus related to material handling (e.g., quarantine, segregation, etc.) and cleaning is warranted when there is an increased risk of toxicity to other species. Assign higher risk to CGMP deviations that could result in toxic exposure to other species, and ensure adequate information is collected to evaluate this risk. (For example, if a CGMP deviation related to cleaning equipment used to process monensin is noted, ensure logs are collected to establish what other drugs were subsequently processed on that equipment. Potential carryover of monensin into a drug used for horses would significantly elevate the risk of health hazard to the horse.)

In addition to the above hazards that are special considerations for Type A medicated articles, these drugs also pose potential hazards common to other drug types if improperly manufactured. Examples include sub-potency (causing lack of efficacy) and impurities (potential toxicity). Also consider the relative risk posed by the manufacturing process and give priority to Type A medicated article(s) with more complex manufacturing processes.

- Most Type A medicated articles are manufactured in a batch format and by simple mixing. These types of manufacturing processes tend to require few or no in-process controls and the critical process parameters often include only order of addition of the ingredients and mixing speed/time. These types of processes are considered lower risk.
- Some Type A medicated articles are manufactured using more complex processes including granulation, spraying of a dissolved API onto an excipient, or continuous manufacturing. These less-common processes are considered higher risk.

Surveillance Inspection Frequency / Depth

For both domestic and foreign firms, CVM determines the risk-based inspection frequency of surveillance inspections based on anticipated field resources, statutory obligations, regulatory requirements, establishment’s compliance history, technology employed, and characteristics of the products. For domestic firms, within each work planning cycle, CVM will identify two tiers of domestic firms for surveillance inspection. Tier 1 firms represent the highest priority for surveillance inspection. Tier 2 firms are lower priority for surveillance coverage. For foreign firms, CVM only identifies one tier for each work planning cycle.

The ORA Program Division is responsible for determining the depth of coverage given to each drug establishment during a surveillance inspection. The CGMP inspectional coverage shall be sufficient to assess the state of compliance for each establishment. When a system is inspected, the inspectional findings pertaining to that system are ordinarily considered applicable to all products which use it. Inspections under this compliance program should cover all systems as specified below. There are significantly fewer CGMP requirements in Part 226 compared to Part 211.

Investigators should select a suitable number and type of products to accomplish adequate coverage of the system. Selection of products should be made so that coverage is representative of the establishments’ overall abilities to comply with CGMP requirements.

Compliance Inspection Frequency / Depth

Domestic Firms: CVM will request the ORA Division initiate a “for-cause” compliance inspection when appropriate. For-cause inspections can be assigned at any time when there is reason to believe a facility has serious manufacturing problems or to investigate a specific problem or product complaint that has come to FDA’s attention. The ORA Program Division can conduct a for-cause inspection on its own initiative (e.g. in response to a FAR, compliance follow-up, or based on information obtained from another center), but should notify CVM via CVMAntimalDrugGMP@fda.hhs.gov in advance for proper coordination and to prevent duplication of efforts.

In general, the ORA Division is responsible for creating and issuing OAI follow-up compliance inspections in accordance with FMD-86. However, ORA Division should contact CVM via CVMAntimalDrugGMP@fda.hhs.gov to confirm CVM does not intend to issue a special follow-up assignment memorandum or have specific concerns for follow-up.

Foreign Firms: CVM is responsible for creating, issuing, and monitoring all foreign OAI follow-up compliance inspection assignments.

Inspectional Coverage: Requirements of Type A Medicated Article Manufacturing

Product Quality Signal Review:

Inspections of Type A medicated articles should include significant coverage of potential adverse product quality signals. Complaints should be covered early during inspection to help guide the scope of coverage.

Complaint Files [21 CFR 226.115](#)

Verify the firm maintains, for a period of 2 years, records of all written or verbal complaints concerning the safety or efficacy of each Type A medicated article(s). The firm's competent and responsible personnel should evaluate all complaints and, where indicated, take appropriate action. Ensure the records document the evaluation and the action.

Review complaints to determine whether they indicate significant or repeated problems. For cases where ORA will recommend an OAI classification, document the connection between complaints and other CGMP issues found during the inspection, and include evidence of relevant complaints in the EIR (e.g., complaint log and individual relevant complaints). If the firm's system for complaint handling is inadequate such that relevant complaints would not be captured, ensure the EIR contains detailed coverage of this deficiency.

Complaint reviews (medical): Check the establishment's written procedures describing how Adverse Drug Experience (ADE) Reports are investigated, evaluated and submitted to FDA, and determine whether they are adequate and followed; refer to 21 CFR 514.80. Also check the complaint files to see whether there are any ADE complaints not submitted to CVM via Form FDA 1932 - Veterinary Adverse Reaction, Lack of Effectiveness, Product Defect Report. Determine if 15-Day reports, required from serious, unexpected ADEs are submitted to FDA within 15 working days.

Complaint reviews (product defects): Examine the product defect reports submitted to CVM via Form FDA 1932. Review that follow-up actions were undertaken. For example, if it is recommended that the batch record be reviewed to assess the number of similar complaints, there should be a report indicating that the batch records have been reviewed and the complaint investigated. Consider further investigation of the batch records when there are repeated reports of the same type of defect.

General Provisions

Personnel [21 CFR 226.10](#)

Throughout the inspection, observe whether personnel performing regulated activities have an appropriate understanding of the processes they are performing. It is essential that key personnel have the appropriate education and/or experience to ensure CGMP oversight of the manufacture and control of Type A medicated article(s). If deficiencies are noted, document the connections between inadequate education/experience of personnel (including consultants) and violative product or other CGMP violations.

Facilities and Equipment

Cross-contamination is a significant concern in a facility that manufactures more than one product. Review the firm's method for separating the products, either by space or time, to ensure there is no potential for cross-contamination. If equipment is not dedicated to one product, review records of cleaning and cleaning validation. If personnel work in more than one area, verify the employees are trained to ensure that they take adequate precautions to prevent cross-contamination when they pass from one area to another. Refer to CP 7356.002M - Human Drugs - Inspections of Licensed Biological Therapeutic Drug Products for additional information regarding cross-contamination and CP 7346.832 - Human Drugs - Preapproval Inspections for additional information regarding highly potent and toxic compounds. [Drug Compliance Programs | FDA](#)

Buildings [21 CFR 226.20](#)

Verify the firm maintains buildings in which Type A medicated article(s) are manufactured, processed, packaged, labeled, or held in a clean and orderly manner and they are of suitable size, construction, and location in relation to surroundings to facilitate maintenance and operation for their intended purpose. Ensure the building provides adequate space for the orderly placement of equipment and materials used in any manufacturing, packaging, labeling, storage or laboratory operation to minimize risk of mix-ups between different Type A medicated article(s), their components, packaging, or labeling.

Ensure the buildings also provide adequate lighting and ventilation, and when necessary for the intended production or control purposes, adequate screening, dust and temperature controls, to avoid contamination of Type A medicated article(s), and to avoid other conditions unfavorable to the safety, identity, strength, quality, and purity of the raw materials and Type A medicated article(s) before, during, and after production. Ensure the firm provides and maintains adequate washing, cleaning, toilet, and locker facilities.

Verify work areas and equipment used for the production of Type A medicated article(s) or for the storage of the components of Type A medicated article(s) are not used for the production, mixing or storage of finished or unfinished insecticides, fungicides, rodenticides, or other pesticides or their components unless such materials are recognized as approved drugs intended for use in animal feeds.

Ensure facility layout and air handling systems are designed for prevention of cross-contamination with any other drugs, particularly highly potent drugs (penicillin, beta-lactams, steroids, hormones, cytotoxic drugs, etc.), if applicable.

Equipment [21 CFR 226.30](#)

With the exception of some minor equipment (e.g., scoops, holding vessels, etc.), the vast majority of equipment used to manufacture Type A medicated articles is either mechanical, automatic, or electronic in nature. The regulations only permit this type of equipment to be used “when adequate inspection and checking procedures or other quality control procedures are used

to assure proper performance.” (See 21 CFR 226.1.) Therefore, a variety of approaches are potentially acceptable for ensuring proper performance of equipment. When inspecting equipment, ask the firm what mechanisms they use to assure proper performance and evaluate whether they are adequate, considering the complexity of the equipment, the risk posed by inadequate performance, and whether any product defects have been caused by improper equipment performance.

Evaluate whether the firm maintains equipment used for the manufacture, processing, packaging, bulk shipment, labeling, holding, or control of Type A medicated article(s) or their components in a clean and orderly manner and ensure equipment are of suitable design, size, construction, and location to facilitate maintenance and operation for its intended purpose. For example, ensure the equipment is constructed so that any surfaces that come into contact with Type A medicated article(s) are not reactive, additive, or absorptive to an extent that significantly affects the identity, strength, quality, or purity. Verify the equipment is constructed so that any substance required for the operation of the equipment, such as lubricants, coolants, etc., may be employed without hazard of becoming an unsafe additive to the Type A medicated article(s).

Determine if scales and weighing equipment used for weighing components are accurate and appropriately calibrated.

Product Quality Control

Production and control procedures [21 CFR 226.40](#)

Ensure the firm has production and control procedures that include all reasonable precautions to assure that the Type A medicated article(s) produced have the identity, strength, quality, and purity they purport to possess. The firm should:

- Verify all automated processes if an automated process is used. Every critical step within the manufacturing process must be performed by one or more competent responsible individuals. Examples of critical steps include, but are not limited to, the selection, weighing, and measuring of components; the addition of drug components during the process; weighing and measuring during various stages of the processing; and the determination of the finished yield.
- Receive, adequately identify, and properly store and handle containers to be used for undiluted drugs, drug components, intermediate mixtures thereof, and Type A medicated article(s) in a manner adequate to avoid mix-ups and contamination.
- Maintain and operate all manufacturing equipment in a manner to avoid contamination of the Type A medicated article(s) and to ensure the integrity of the finished product.
- Establish and follow procedures for evaluating batch discrepancies and failures to meet specifications prior to release. The firm should thoroughly investigate questionable batches, including those before and after the discrepancies or failures.

- Establish and follow procedures for cleaning equipment to avoid contamination of Type A medicated article(s). Place inspectional focus on equipment coming into contact with the drug component of the Type A medicated article. Many excipients in Type A medicated articles are ingredients permitted to be used in animal feeds, so thorough cleaning of equipment that contacts only the excipients is typically less critical. The firm should have sufficient safeguards to avoid any buildup which would cause out of specification assay results and/or cross-contamination in any of the subsequent batches of the Type A medicated article(s). Determine and document in the Establishment Inspection Report (EIR) the apparent effectiveness of the firm's procedures for clean-out and prevention of cross-contamination.

Components [21 CFR 226.42](#)

Assess whether the firm receives, examines or tests, stores, handles, and otherwise controls drug components, including undiluted drugs and any intermediate mixes containing drugs used in the manufacture and processing of Type A medicated article(s), in a manner to maintain the integrity and identification of such articles. Ensure the firm maintains receipt and inventory records for a minimum of 2 years and the records show the origin of any drug components, the manufacturer's control number (if any), the dates and batches in which they were used, and the results of any testing of them.

Verify the firm stores and handles non-drug components in a manner to avoid contamination, including cross-contamination from manufacturing operations.

Laboratory Controls [21 CFR 226.58](#)

Verify the firm has established adequate specifications and test procedures to assure that the drug components and the Type A medicated article(s) conform to appropriate standards of identity, strength, quality, and purity. If significant deviations are noted regarding specifications and testing methods for the drug components and/or the firm's practices regarding the testing, document in the EIR. The firm must have master records containing appropriate specifications and a description of the test procedures used to check them for each kind of drug component used in the manufacture of Type A medicated article(s). This may consist of the manufacturer's or supplier's statement of specifications and methods of analyses. Confirm the firm has specifications for Type A medicated article(s) and a description of necessary laboratory test procedures to check such specifications.

Also, the firm must assay representative samples of finished Type A medicated article(s). For Type A medicated article(s) manufactured from an undiluted drug, the firm must assay each batch for its drug component(s). For Type A medicated article(s) manufactured by dilution of another Type A medicated article(s) for which each batch has been assayed, the firm must assay the first five consecutive batches for their drug component(s). Once five consecutive batches assay within the limitations, the firm must assay representative samples of not less than 5 percent of all batches produced. When any batch does not assay within limitations, each batch should again be assayed until five consecutive batches are within limitations.

Verify the firm has established that the drug components remain uniformly dispersed and stable in the Type A medicated article(s) under ordinary conditions of shipment, storage, and use. This may consist of a determination on a Type A medicated article(s) of substantially the same formula and characteristics. Verify and document in the EIR deviations noted in the firm's methods for stability determination and that suitable expiration dates appear on the labels of the Type A medicated article(s) to assure that the articles meet the appropriate standards of identity, strength, quality, and purity at the time of use. If needed, contact CVM Office of New Animal Drug Evaluation, Division of Manufacturing Technologies, to confirm approved product specifications, test procedures and expiration dates via CVMAnimalDrugGMP@fda.hhs.gov.

Ensure the firm has adequate provision to check the reliability, accuracy, and precision of any laboratory test procedure used. The official methods in "Methods of Analysis of the [Association of Official Analytical Chemists](#)," methods described in an official compendium, and any method submitted as a part of a food additive petition or NADA/ANADA that has been accepted by the Food and Drug Administration meet this provision. In other words, validation of methods for API and finished Type A medicated articles are submitted to CVM as part of the NADA or ANADA. However, during the inspection if the investigator has concerns about test methods they can contact CVM's Office of New Animal Drug Evaluation via CVMAnimalDrugGMP@fda.hhs.gov.

Ensure the firm has provisions for the maintenance of the results of any assays, including dates and endorsement of analysts. The firm must retain those records for at least 2 years after distribution by the manufacturer of the Type A medicated article(s) has been completed.

Packaging and Labeling [21 CFR 226.80](#)

Historically, missing or misprinted lot numbers or expiration dates on drug labels is a common manufacturing error and has resulted in product recalls. It is essential that controls be in place to minimize labeling errors and ensure accurate labeling.

During an inspection, verify the firm has adequate controls for packaging and labeling operations. Review of the complaint files can help identify deficiencies in specific products or processes such as missing, incorrect or illegible labels or leaking containers. For example, assure that:

- Only those Type A medicated article(s) that have met the specifications established in the master-formula records are distributed.
- Controls are in place to prevent mix-ups during the packaging and labeling operations and storage of labeling.
- Correct labeling is employed for each Type A medicated article(s) to include lot or control numbers that permit determination of the history of the manufacture and control of the batch of Type A medicated article(s). If significant deviations are noted, document in the EIR the lot or batch numbering system used and why it is insufficient to identify batch production history.

- Verify label control and reconciliation in order to ensure adequate control over the quantities of labeling issued, and quantities of labeling used for the Type A medicated article(s). Select one or more product label/s and confirm the count matches the firm's records.
- Confirm the firm distributes Type A medicated article(s) in suitable containers to ensure the safety, identity, strength, and quality of the finished product.

If needed, contact CVM Office of New Animal Drug Evaluation, Division of Manufacturing Technologies, to confirm approved product labeling and container-closure systems via CVMAnimalDrugGMP@fda.hhs.gov.

Records and Reports

Distribution Records [21 CFR 226.110](#)

Ensure the firm maintains complete records for each shipment of Type A medicated article(s) in a manner that will facilitate a recall, diversion, or destruction of the Type A medicated article(s), if necessary. Verify the firm retains records for at least 2 years after the date of the shipment by the manufacturer and the records include the name and address of the consignee, the date and quantity shipped, and the manufacturing dates, control numbers, or marks identifying the Type A medicated article(s) shipped.

Master Formula Records [21 CFR 226.102\(a\)](#)

When conducting inspection review of Master Formula Records, verify the adequacy of manufacturing instructions and completeness and accuracy of the documents. Also confirm that for each Type A medicated article(s), a competent and responsible individual prepares, endorses, and dates master-formula records and a second competent and responsible individual independently checks, reconciles, endorses, and dates them.

The master formula record must include the name of the Type A medicated article(s) and a specimen copy of its label and the weight or measure of each ingredient, adequately identified, to be used in manufacturing a stated weight of the Type A medicated article(s). Review a representative number of master formula records to determine if calculations regarding the final drug levels are correct.

The record must also include a complete formula for each batch size, or of appropriate size in the case of continuous systems to be produced from the master-formula record, including a complete list of ingredients designated by names or codes sufficiently specific to indicate any special quality characteristics.

An accurate statement of the weight or measure of each ingredient must appear in the record, except that reasonable variations may be permitted in the amount of ingredients necessary in the preparation of the Type A medicated article(s), provided that the variations are stated in the

master formula. The record also must include an appropriate statement concerning any calculated excess of an ingredient, and a statement of the theoretical yield.

Manufacturing instructions must be defined for each type of Type A medicated article(s) produced on a batch or continuous operation basis, including mixing steps and mixing times that have been determined to yield an adequately mixed Type A medicated article(s). In the case of Type A medicated article(s) produced by continuous production run, the record also must define any additional manufacturing directions including, when indicated, the settings of equipment that have been determined to yield an adequately mixed Type A medicated article(s) of the specified formula. This is important because content uniformity testing is not routinely performed for Type A medicated articles, so adherence to the approved manufacturing instructions is the only assurance of a homogeneous product.

Also check for control instructions, procedures, specifications, special notations, and precautions to be followed. If needed, contact CVM Office of New Animal Drug Evaluation, Division of Manufacturing Technologies, to confirm approved product master formula records via CVMAnimalDrugGMP@fda.hhs.gov.

Separate Batch-Production and Control Records [21 CFR 226.102\(b\)](#)

Ensure a separate batch-production and control record is prepared for each batch or run of Type A medicated article(s) produced and is retained for at least 2 years after distribution by the manufacturer has been completed. Verify the batch-production and control record conforms to master formula requirements and includes:

- product identification
- date of production
- endorsement by a competent and responsible individual
- records of each step in the manufacturing, packaging, labeling, and controlling of the batch, including
 - dates
 - specific identification of drug components used
 - weights or measures of all components
 - laboratory-control results
 - mixing times
 - a determination of theoretical vs. actual batch yield
 - the endorsements of the individual actively performing or the individual actively supervising or checking each step in the operation
- a batch number that permits determination of all laboratory-control procedures
- results on the batch and all lot or control numbers appearing on the labels of the Type A medicated article(s).

Investigation of Downstream Consignee/User Licensure

Inspection of Type A medicated article manufacturers is the agency’s primary mechanism for enforcing the medicated feed mill license requirements ‘downstream’ of the Type A manufacturers. Due to the risk of drug residues, all medicated feed mill that use Category II Type A medicated articles must be licensed by FDA as feed mills.⁴ (See [21 CFR 558.4](#) for the requirement and charts designating Category I vs II.) Therefore:

- 1) Identify which Type A medicated articles produced by the firm are Category II.
- 2) Select a representative sample of Category II Type A medicated articles (covering at least 5 products, unless the firm produces fewer than 5, in which case, all products are expected to be covered).
- 3) Obtain customer lists and distribution records for each of the selected articles
- 4) For all consignees, ensure the Type A medicated article manufacturer has an unrevoked written statement from the consignee asserting that the consignee is either a licensed feed mill or will only ship to feed mills with approved licenses [21 CFR 510.7](#)
- 5) At minimum, document the Type A medicated articles selected and time periods reviewed in the EIR.

Special Topics

Data Integrity

Data integrity refers to the completeness, consistency, and accuracy of data and **applies to all systems**. Complete, consistent, and accurate data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate (ALCOA). Maintaining the integrity of data is critical throughout the CGMP data life cycle, including in the creation, modification, processing, maintenance, archival, retrieval, transmission, and disposition of data after the record’s retention period ends. System design and controls should enable ease of verifying the authenticity of the data as well as detection of errors, omissions, and aberrant results throughout the data’s life cycle.

FDA expects that all data be reliable and accurate. CGMP regulations and guidance allow for flexible and risk-based strategies to prevent and detect data integrity issues.⁵ Firms should implement meaningful and effective strategies to manage their data integrity risks based on their process understanding and knowledge management of technologies and business models.

⁴ For an overview of medicated feed mill licensing requirements:

<https://www.fda.gov/animal-veterinary/animal-food-feeds/medicated-feeds>

⁵ See Guidance for Industry - Data Integrity and Compliance With Drug CGMP Questions and Answers Guidance for Industry. Note that this guidance is intended to clarify CGMP “as required in 21 CFR parts 210, 211, and 212,” but some concepts within the guidance are useful to inspecting data integrity for other drugs, including Type A medicated articles.

When evaluating whether a firm is meeting regulatory requirements, it may be useful for an investigator to consider the following:

- What controls are in place to assure that data is complete?
- Are activities documented at the time of performance?
- Are activities attributable to a specific individual?
- Can only authorized individuals make changes to records?
- Is there a record of changes to data?
- Are records reviewed for accuracy, completeness, and compliance with established standards?
- What controls are in place to assure data is securely maintained from data creation through disposition after the record's retention period?
- Is the data securely stored to be protected against any natural disasters or catastrophic system failure?
- Is the stored data backed up to avoid data loss in case of any natural disasters or catastrophic system failure?
- Is the stored data routinely evaluated for retrievability, accuracy, completeness and to assure there is no data loss?
- Is scientific rational/justification used to support investigational root causes and conclusions?

The following are possible indications of data integrity problems:

- Alteration of raw, original data and records (e.g., the use of correction fluid)
- Inconsistencies in manufacturing documentation (e.g., identification of actual equipment used) and other information in the submission.
- Multiple analyses of assay using the same sample without adequate justification.
- Exclusion of specific lots from the stability program to avoid submitting failed results.
- Reworking or process modifications not adequately justified or appropriately reported.
- Manipulation of a poorly defined analytical procedure and associated data analysis to obtain passing results.

- Backdating stability test results to meet required commitments.
- Fabrication of acceptable test results without performing the test.
- Use of test results from previous batches to substitute testing for another batch.⁶

Profiling

The inspection findings will be used as the basis for updating the Type A medicated article profile class, “TAM,” via eNSpect.

Refusals

Under Section 501(j) of the FD&C Act, a drug is adulterated that “has been manufactured, processed, packed, or held in any factory, warehouse, or establishment and the owner, operator, or agent of such factory, warehouse, or establishment delays, denies, or limits an inspection, or refuses to permit entry or inspection.” See “Guidance for Industry - Circumstances that Constitute Delaying, Denying, Limiting or Refusing a Drug Inspection” for additional information.

Investigators should fully document the circumstances of the denial/delay/limitation/refusal. The ORA Program Division should attempt to resolve the issue, but if initial attempts are unsuccessful, the ORA Division should notify CVM Compliance for awareness and assistance. In the event a denial/delay/limitation/refusal occurs during an inspection where the circumstances indicate a significant threat to the health to humans or animals, the investigator should attempt to collect an inventory of all drugs (components and finished products) at the establishment.

Sampling

Samples of defective product constitute persuasive evidence that significant CGMP problems exist. Physical samples may be an integral part of a CGMP inspection where control deficiencies are observed. Physical samples should be correlated with observed control deficiencies. Consider consulting your servicing laboratory for guidance on quantity and type of samples (in-process or finished) to be collected. Documentary samples may be submitted when the documentation illustrates the deficiencies better than a physical sample. Divisions may elect to collect, but not analyze, physical samples, or to collect documentary samples to document CGMP deficiencies. Physical sample analysis is not necessary to document CGMP deficiencies.

When a large number of products have been produced under deficient controls, collect physical and/or documentary samples of products which have the greatest therapeutic significance, narrow margin of safety, or a high dosage strength. Include samples of products of minimal therapeutic significance only when they illustrate highly significant CGMP.

⁶ This question refers to inappropriate substitution of data in a firm’s records and should not be confused with qualifying for a reduced assay testing requirement based on previous test results under 21 CFR 226.58(c)(2).

Inspection Teams

An inspection team (See IOM section 5.1.2.5), composed of experts from within the Division, other Divisions, or Headquarters, is encouraged when it provides needed expertise and experience. Contact ORA/OMPTO/OPQO/ Pharmaceutical Quality Programs Branch (PQPB) if technical assistance is needed (See also [FMD 142](#)). Participation of an analyst (chemist or microbiologist) on an inspection team is also encouraged, especially where laboratory issues are extensive or complex. Contact your Drug Servicing Laboratory or ORA ORS/OMPSLO (Office of Medical Products and Specialty Lab Operations).

Reporting

The Investigator will utilize Section 5.2.3 of the IOM for guidance in reporting of inspectional findings. Identify “systems” covered in the Summary of Findings. Add additional information as needed or desired, for example, a description of any significant changes that have occurred since previous inspections.

For all inspections recommended for OAI classification by the field, include as exhibits the firm’s complaint log(s) and/or adverse event log(s), as well as individual records of any complaints/AEs that may be related to CGMP deficiencies, regardless of whether complaint handling or adverse event reporting itself is cited on the FDA-483.

Reports with specific and specialized information required should be prepared as instructed within the individual assignment/attachment.

PART IV – ANALYTICAL

Analyzing Laboratories

Contact ORSOMPSLOProgramCoordinators@fda.hhs.gov for servicing laboratories for all chemical and microbiological testing. When contacting ORS/OMPSLO for servicing laboratories, provide product description, lots to be tested, analyses to be performed, and reason for the sample collection. Servicing laboratories will be identified based on lab specialization, technology and testing expertise, and laboratory capacity.

[NOTE: The Laboratory Servicing Table (LST) Dashboard is not sufficiently detailed to accurately identify laboratories and should not be used for selecting servicing laboratories under this program.]

Analyses to be Conducted

The types of typical analyses that may be performed under this program include (but are not limited to):

- Routine chemical analyses: Assay, Impurities, Identification
- Routine microbiological analyses: Sterility, Endotoxin, Nonsterile examination

Samples are to be examined for compliance with applicable specifications as they relate to deficiencies noted during the inspection.

Methodology

All analyses should be performed by the official regulatory methods, or when no official method exists, by other validated procedures identified by ORS/OMPSLO.

PART V - REGULATORY/ADMINISTRATIVE STRATEGY

When non-compliant conditions are identified which demonstrate that an establishment is not operating within a state of control, all voluntary, advisory, and/or judicial options currently available to the Agency should be considered. In most cases, enforcement actions should be based on patterns of significant deviations, which have been fully documented, and for which prior notice has been given. Generally, enforcement actions are recommended when a firm is unwilling or unable to voluntarily correct violations. However, FDA may take immediate action without prior notice in the circumstances outlined in RPM 4-1-1, especially in those cases where action (e.g., administrative detention, seizure) is needed to prevent serious harm. A plan to achieve voluntary compliance should be developed as appropriate before recommending an enforcement action to correct a violation. All corrective action approaches in domestic establishments are monitored and managed by the ORA Division. The approaches may range from shut down of operations, recall of products, conducting testing programs, development of new procedures, modifications of plants and equipment, to simple immediate corrections of conditions. CVM/OSC/Division of Drug Compliance will assist the ORA Division as requested.

Evidence to support a single significant deficiency or a trend of significant deficiencies within any given system or systems covered during an inspection could constitute the failure of a single system or multiple systems. The significant failure of any one system warrants consideration of an out-of-control determination for all the establishment's operations affected by such failure. Until an establishment is in compliance, any pending or future NADA/ANADA(s) affected by the system(s) failure may not be approved.

The risk to humans and animals and the nature of the CGMP deviations are highly important in determining an appropriate course of action. Divisions may wish to consult with CVM/OSC/Division of Drug Compliance for guidance in developing compliance strategy. Determining the most effective and efficient way to protect animals and the consuming public is foremost in considering any action. The Regulatory Procedures Manual (RPM) should be consulted and followed in submitting any recommendation for regulatory action.

For example, in situations where there is no immediate risk to human or animal health and where voluntary correction should be pursued, an Untitled Letter may be used. In other situations, a Warning Letter may be appropriate. The establishment's response to a Warning Letter should include all actions it plans to take to achieve voluntary compliance and the time frames for completion. If this does not achieve the desired compliance result, a subsequent regulatory action (seizure/injunction) should be considered.

When the deviations are serious and/or there is reasonable likelihood of immediate risk to human or animal health, administrative detention or seizure should be considered. In some situations, a recall may also be appropriate. Those establishments with a long history of significant repetitive and/or ongoing violations, which are unlikely to be corrected, are strong candidates for an injunction. Violators with intent to defraud or those deemed appropriate under the factors described in RPM 6-5-3 may also be considered for criminal prosecution.

FDA laboratory tests that demonstrate the effects of absent or inadequate CGMP are strong evidence for supporting regulatory actions. Such evidence development should be considered as an inspection progresses and deficiencies are found. However, no sampling or laboratory testing is necessary for CGMP adulteration charges.

All compliance actions, (excluding VAI regulatory meetings held at the ORA Division's discretion) require CVM concurrence.

Significant Failures – CGMP

When deciding the type of action to recommend, the initial decision should be based on the seriousness and/or the frequency of the problem. Examples of significant failures to follow CGMP include, but are not limited to the following:

- (226.30) Scales and weighing equipment used for weighing components are not accurate.
- (226.30, 226.40) Common mixing and handling equipment is used for different Type A medicated articles, but the effectiveness of the firm's procedures for clean-out and prevention of cross-contamination and is inadequate and/or mixing and handling equipment is not constructed to facilitate clean-out.
- (226.20) Pesticides not intended for animal feed use and/or toxic materials are stored, handled, or manufactured in common equipment or work areas where contamination could occur
- (226.42) The firm's practices regarding labeling of components, intermediates, and finished Type A medicated articles (including containers or bins) are inadequate to prevent mix-ups.
- (226.42) The firm's procedures for receipt, testing, and control of drug components are inadequate to ensure integrity and identification of such articles
- (226.58) Specifications and testing methods for components and Type A medicated articles are not established.
- (226.102) Master formula records do not exist, have not been reviewed and endorsed, or do not contain adequate manufacturing instructions.
- (226.102) Master formula records contain incorrect weights, measures, or instructions that could result in incorrect levels of drug components in the finished Type A medicated article.
- (226.40) Critical steps in the production process related to the master formula were not followed.
- (226.102) Batch records are not kept.

- (226.40) Batch records have not been reviewed by responsible personnel for discrepancies between theoretical and actual batch yield made or significant discrepancies were noted but responsible personnel did not prevent distribution of potentially impacted batches
- (226.58) Suitable expiration dates were not assigned and included on the labels of Type A medicated articles.
- (226.80) Batch numbers are not included on labels, or the batch numbering system is not adequate to identify complete batch production history.
- (226.58) Finished Type A medicated article assays are not performed in accordance with 226.58(c).
- (226.115) Inadequate records are maintained of complaints, evaluations, and actions taken, or failure to take appropriate action.

In addition to 501(a)(2)(B) violations for CGMP violations, FDA will consider:

- 501(a)(5) violations for failure to have appropriate marketing authorization
- 501(c) violations for potency and purity that differ from the product's labeling.
- 502(f)(1) violations for inadequate directions for use; and
- 502(f)(2) violations for Type A medicated articles that do not have required warnings as are necessary for protection of the users, e.g., precautions for handlers.

Classification

Inspection classifications are based on the public health significance and the facility's response and include "No Action Indicated (NAI)," "Voluntary Action Indicated (VAI)," and "Official Action Indicated (OAI)." For additional information, see FMD-86 Establishment Inspection Report Conclusions and Decisions. ORA has final classification authority for all NAI and VAI inspections. For inspections proposed to be classified as OAI, the ORA Division should submit any recommendation for regulatory follow-up via CMS. If CVM deems an inspection recommended OAI by ORA should be reclassified (e.g., VAI), CVM will provide written justification to ORA. If ORA disagrees, a meeting will be scheduled between the ORA OPQO Division Compliance Branch and CVM's Division of Drug Compliance to determine the appropriate final classification.

The following are examples of situations that may warrant inspectional classifications and/or compliance actions and is not an all-inclusive list:

No Action Indicated (NAI):

- No objectionable conditions or practices were found during the inspection (or the significance of the documented objectionable conditions found does not justify further action).

Voluntary Action Indicated (VAI)

- Objectionable conditions were found and documented, but FDA is not prepared to take or recommend official action since the objectionable conditions do not meet the threshold for regulatory action. This includes inspections where significant adverse conditions were observed, but the facility provides an adequate response or corrective action plan within established timeframes (e.g., during the inspection or 15 working days after the issuance of a Form FDA 483).

Official Action Indicated (OAI)

- Significant adverse conditions are observed, and the facility does not provide an adequate response or corrective action plan that demonstrates effectiveness and consistent implementation within established timeframes (e.g., no adequate corrective actions taken during inspection or reported after 15 working days).
- If an inspection report documents that one or more systems at the establishment is/are out of control, the inspection should receive an initial OAI classification. Issuance of a Warning Letter or taking other regulatory action is appropriate unless adequate corrective actions have been implemented.
- Significant and wide-spread adverse conditions that are observed to directly affect Type A medicated articles
- Systemic breakdown in any system that is likely to result in human or animal health hazard(s).
- Analytical results from FDA official samples indicating a Type A medicated article is adulterated (and the facility did not independently identify and correct the issue prior to distributing the product).
- Despite reasonable attempts to inspect, the firm delays, denies, or limits an inspection, or refuses to permit entry or inspection.

Imports

Foreign establishment inspection reports are provided to CVM from the Office of Medical Products and Tobacco Operations (OMPTO). CVM reviews the establishment inspection findings, and, when indicated by review of the findings, recommends to ORA's Office of Enforcement and Import Operations/DIO that a firm be subject to Detention Without Physical Examination (DWPE). These cases are processed electronically in CMS.

Recommendations for addition to DWPE based on establishment inspections follow the guidance in Regulatory Procedures Manual (RPM), Chapter 9-8-12, "[RECOMMENDATIONS BASED ON ESTABLISHMENT INSPECTION](#)". Violations may include deviations from CGMP, insanitary conditions, or other practices that may cause articles to be misbranded, adulterated, or otherwise in violation of the FD&C Act per section 801(a). For example, if a foreign

establishment or foreign government refuses a foreign inspection, the firm and its products may be subject to DWPE because the drug is adulterated under section 501(j). To remove a firm's product from the Red List of an import alert, information should be provided to the Agency to adequately demonstrate that the firm has resolved the condition that gave rise to the appearance of the violation so the agency will have confidence that future entries will be in compliance with the FD&C Act. For guidance on removal from detention without physical examination, refer to FDA's Regulatory Procedures Manual, Chapter 9-8, "Detention without Physical Examination (DWPE)". Additionally, import alerts may provide specific requirements for removal from DWPE. See Import Alerts, including:

- #66-40: "DETENTION WITHOUT PHYSICAL EXAMINATION OF DRUGS FROM FIRMS WHICH HAVE NOT MET DRUG GMPS"
- #68-19: "DETENTION WITHOUT PHYSICAL EXAMINATION OF UNAPPROVED FINISHED NEW ANIMAL DRUGS"
- #66-79: "DETENTION WITHOUT PHYSICAL EXAMINATION OF DRUGS FROM FOREIGN ESTABLISHMENTS REFUSING FDA INSPECTION"

See additional information on importation of animal drugs at the following URL: [Animal and Veterinary Products | FDA](#)

Exports

Section 801(e)(1) of the FD&C Act provides that unapproved new animal drugs may be exported if they meet certain conditions. Export certificates are issued by CVM/OSC/Division of Drug Compliance. For additional information see Guidance for Industry - FDA Export Certificates at the following URL: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-export-certification>

PART VI - REFERENCES AND PROGRAM CONTACTS

References

1. Federal Food, Drug, and Cosmetic Act, as amended (the Act) [21 U.S.C. 301 *et seq.*] [Federal Food, Drug, and Cosmetic Act \(FD&C Act\) | FDA](#)
2. Code of Federal Regulations, Title 21, including, but not limited to Parts 11, 210, 226, 510.7, and 558 [Electronic Code of Federal Regulations \(eCFR\)](#)

21 CFR Part 226, Current Good Manufacturing Practice Regulations for Type A Medicated Articles;

21 CFR Part 558, New Animal Drugs for Use in Animal Feed. This reference identifies NADA approved drug articles. It also provides sponsor Nos. for manufacturers listed in Section 510.600(c).

21 CFR 558.4(b) includes a listing of Category II (high therapeutic risk) and Category I (low therapeutic risk) drug product

21 CFR Part 510.7, Consignees of New Animal Drugs for Use in the Manufacture of Animal Feed.
3. Animal Drugs at FDA [Animal Drugs @ FDA](#)
4. Compliance Policy Guides Manual, Chapter 6 - Veterinary Medicine [Chapter 6 - Veterinary Medicine | FDA](#)
5. Regulatory Procedures Manual (RPM) [Regulatory Procedures Manual | FDA](#)
6. Investigations Operations Manual (IOM) [Investigations Operations Manual | FDA](#)
7. Inspection Guides [Inspection Guides | FDA](#)
8. Guidance for Industry – CVM [Guidance for Industry | FDA](#)
9. Guidance for Industry - FDA Form 483 Frequently Asked Questions <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/fda-form-483-frequently-asked-questions>
10. Guidance for Industry - Circumstances that Constitute Delaying, Denying, Limiting or Refusing a Drug Inspection [Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection | FDA](#)
11. Guidance for Industry - Data Integrity and Compliance With Drug CGMP Questions and Answers Guidance for Industry [Data Integrity and Compliance With Drug CGMP Questions and Answers Guidance for Industry | FDA](#)

12. ICH Quality Guidelines <https://www.ich.org/page/quality-guidelines>, including, but not limited to:
 - Q9 Quality Risk Management
 - Q10 Pharmaceutical Quality System
13. The United States Pharmacopoeia / National Formulary (USP/NF) – [U.S. Pharmacopeia \(usp.org\)](https://www.usp.org); <https://fda.sharepoint.com/sites/OIMT-FDAL-Library/SitePages/USP-NF.aspx>
14. [FMD 86: Establishment Inspection Report Conclusions and Decisions \(fda.gov\)](https://www.fda.gov/oc/ohrt/fmd86)
15. [FMD 142](https://www.fda.gov/oc/ohrt/fmd142) - Technical Assistance
16. Compliance Program: 7356.002 – Drug Manufacturing Inspections ([CDER Compliance Programs – fda.gov](https://www.fda.gov/oc/ohrt/cder-compliance-programs))
17. Compliance Program: 7356.002A – Sterile Drug Process Inspections ([CDER Compliance Programs – fda.gov](https://www.fda.gov/oc/ohrt/cder-compliance-programs))
18. Compliance Program: 7356.002F – Active Pharmaceutical Ingredients ([CDER Compliance Programs – fda.gov](https://www.fda.gov/oc/ohrt/cder-compliance-programs))
19. Compliance Program: 7356.002M – Surveillance Inspections of Protein Drug Substance Manufacturers ([CDER Compliance Programs – fda.gov](https://www.fda.gov/oc/ohrt/cder-compliance-programs))
20. Compliance Program: 7346.832 -Human Drugs - Pre-Approval Inspections/Investigations ([CDER Compliance Programs – fda.gov](https://www.fda.gov/oc/ohrt/cder-compliance-programs))
21. Compliance Program: 7368.001 – Pre-Approval Inspections: New Animal Drug Applications (NADA); Abbreviated New Animal Drug Applications (ANADA); Investigational New Animal Drug (INAD) Applications; Generic Investigational New Animal Drug (JINAD) Applications; Conditional New Animal Drug Applications (CNADA) ([CVM Compliance Programs – fda.gov](https://www.fda.gov/oc/ohrt/cvm-compliance-programs))
22. Compliance Program 7371.001 – Animal Drug Manufacturing Inspections ([CVM Compliance Programs – fda.gov](https://www.fda.gov/oc/ohrt/cvm-compliance-programs))

CVM Contacts

For questions regarding Compliance Program matters, guidance on regulatory action, policy or requests for guidance on CGMP, contact:

CVM/OSC/Division of Drug Compliance
E-mail address: CVMAAnimalDrugGMP@fda.hhs.gov

For questions regarding product requirements per the NADA/ANADA, contact

CVM/ONADE/Division of Manufacturing Technologies
E-mail address: CVMAAnimalDrugGMP@fda.hhs.gov

For questions regarding guidance on New Animal Drug status of marketed drug products, drug listing or registration requirements, or drug shortages contact:

CVM/OSC/Division of Drug Compliance
E-mail Address: CVMSurveillance@fda.hhs.gov

For questions on product defect and adverse drug experience (ADE) reporting requirements, and the [FDA Form 1932](#) - Veterinary Adverse Drug Reaction, Lack of Effectiveness, Product Defect Report contact:

CVM/OSC/Division of Drug Compliance
E-mail Address: CVMAESupport@fda.hhs.gov

ORA Contacts

Investigations Contact:

Pharmaceutical Quality Program Branch
Office of Pharmaceutical Quality Operations
E-mail Address: ORAHQDrugInspectionPOC@fda.hhs.gov

ORS Contact (Microbiology and Chemistry):

ORA/Office of Medical Product and Specialty Lab Operations
E-mail Address: ORSOMPSLOProgramCoordinators@fda.hhs.gov

PART VII - CENTER RESPONSIBILITIES

CVM's Division of Compliance is responsible for the maintenance, review, and revision of the compliance program; and will determine program priorities and recommend program changes. The Division of Compliance will also utilize information obtained by the program evaluations to promote consistency and continuity of inspectional approach and inspectional outcomes across all Pharma Divisions. CVM will continue to provide "real time" ORA inspectional assistance when encountering violative inspections, violative sample collections, for-cause follow-up, and assistance with policy guidance when warranted and as outlined in this Compliance Program.

Please send any comments on the operation and efficiency of this program to the Compliance Program Manager at CVMAntimalDrugGMP@fda.hhs.gov