

FOOD AND DRUG ADMINISTRATION

COMPLIANCE PROGRAM

PROGRAM

7371.001

CHAPTER 71 - Animal Drug Manufacturing Inspections

SUBJECT: Animal Drug Manufacturing Inspections	IMPLEMENTATION DATE 11/19/2021
	COMPLETION DATE Continuing
DATA REPORTING	
PRODUCT CODES	PRODUCT/ASSIGNMENT CODES
All Animal Drugs Industry codes: 54, 56, 60-66, 68	Domestic and Foreign Current Good Manufacturing Practice (CGMP) Inspections: 71001 GMP/NON-GENERIC 71001A NON-GMP 71001B GMP/GENERIC 71001F ACTIVE PHARMACEUTICAL INGREDIENT

FIELD REPORTING REQUIREMENTS

A. Advance Notification

The Center for Veterinary Medicine (CVM) encourages open communication regarding Compliance Program (CP) 7371.001 establishment inspections to mitigate risk, maximize resources and increase work efficiency. CP 7371.001 requires advance notification to FDA management during inspections when investigators reveal significant CGMP deviations and safety risks which could result in a regulatory action (e.g., warning letter, seizure, and injunction) or a withhold recommendation for a new animal drug. In these cases, advance notification should be given before the issuance of the Form FDA-483, Inspection Observations, while the inspection is still in progress. If any significant adverse conditions which could result in regulatory action (e.g. warning letter, seizure, and injunction) are observed, ORA's Program Division should immediately inform CVM's Animal Drug Program Team (ADPT) (HFV-233) via CVMAnimalDrugGMP@fda.hhs.gov.

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

B. eNSpect Reporting

The ORA Division is responsible for completing the Establishment Inspection Report (EIR) with the initial inspection classification, within ORA's established timeframes, consistent with Field Management Directive (FMD) 86, FDA policies governing pharmaceutical quality, and this compliance program. The ORA Division files the inspection documents electronically no later than 45 calendar days from the close of the inspection using the specific module (eNSpect, and/or Compliance Management System (CMS)) accessible to both ORA and CVM.

When both CDER and CVM identify a firm for surveillance coverage only one CGMP inspection (FDA, Mutual Recognition Agreement (MRA), etc.) is required for establishments manufacturing both human and animal drugs. In these cases, time should be divided between both the human and animal compliance programs and reported into eNSpect [enspect.fda.gov] as applicable to the risk associated with the products under inspection and the resources of the investigator.

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

- A. Charge time for CGMP inspections to PAC 71001.
- B. Charge time for non-CGMP investigations or inspections to PAC 71001A.
- C. Charge time for CGMP inspections of generic drug establishments to PAC 71001B.
- D. Charge time for Active Pharmaceutical Ingredient (API) to 71001F

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PART I – BACKGROUND

A primary mission of the FDA (the Agency) is to regulate the manufacturing and distribution of drugs and drug products 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 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:

- 1) evaluating establishments, sterile and non-sterile finished dosage form animal drugs, drug components, and APIs 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, and drug experience reports).

CP 7371.001 Animal Drug Manufacturing Inspections provides guidance for implementing the strategies and captures risk-based inspectional requirements for drug manufacturing.¹ Drugs are of an acceptable quality when manufacturing establishments are operating in a state of control. CP 7371.001 enables FDA to assess whether a firm is operating within a state of control, in an effort to ensure manufacturing processes continue to produce safe and effective drugs, comply with CGMP, and requirements of New Animal Drug Applications (NADA), Abbreviated New Animal Drug Applications (ANADA), the Act and the CFR; and provides for follow-up compliance as well as routine surveillance.²

Animal drugs are not covered under the Drug Supply Chain Security Act (DSCSA). Thus, the product tracing, verification, and product identifier requirements for certain finished human prescription drugs do not apply.

The term “active pharmaceutical ingredient” (API) is used in this program consistent with the meaning of this term as defined in ICH Q7. An active pharmaceutical ingredient is “any substance or mixture of substances intended to be used in the manufacture of a drug product and that, when used in the production of a drug, becomes an active ingredient in the drug product. Such substances are intended to furnish pharmacological activity or other direct effect

¹ CP 7371.001 applies to manufacturing operations of animal drugs but does not apply to Type A medicated articles and medicated feeds. Guidance for Type A Medicated Articles is located in CP 7371.005, and Guidance for Medicated Feed Type B and Type C Manufacturing is found in CP 7371.004. For the purposes of CP 7371.001, “drugs” include APIs and finished dose form animal drug products regulated under 21 CFR Part 211.

² The Center for Veterinary Medicine is also responsible for the regulation of veterinary medical devices and diagnostic aids. CVM does not have pre-marketing approval or CGMP authority over these types of products; therefore, the Center relies in part on Field surveillance conducted under this program to detect violations.

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in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body.” Currently, other terms are also used by FDA and industry to mean an API, including “drug substance” (and bulk drug substance, “BDS”). The use of these terms to describe active pharmaceutical ingredients may be considered equivalent to the term used here, API.

FDA oversight of the manufacture of APIs is important to ensuring the quality of finished drug products. This compliance program covers API manufacturing, which is typically a multi-part process including steps such as chemical synthesis and/or fermentation, purification, crystallization, drying, milling, packing, labeling, and testing.

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.

PART II - IMPLEMENTATION**2.1 – OBJECTIVES**

The goal of this compliance program's activities is to minimize animals' exposure to adulterated drugs and human exposure to adulterated food, resulting from animals treated with adulterated drugs. This includes APIs and finished dose form (sterile and non-sterile) animal drugs.

Under this program, inspections, investigations, sample collections, sample analyses, and regulatory activities are performed:

- to determine whether inspected establishments and animal drugs comply with the FD&C Act's requirements, including CGMP;
- to provide CGMP assessment which may be used in determination of acceptability of the establishment, including the pre-approval review of establishments for New Animal Drug Applications and Abbreviated New Animal Drug Applications (NADAs/ANADAs);
- to provide input to establishments to facilitate their voluntary compliance with the Act; and,
- to protect human and animals from potentially harmful products.

2.2 – STRATEGY**A. Risk-Based Inspection**

Drugs are manufactured using many physical operations to bring together components, containers and closures that are released for distribution. Activities found in establishments can be organized into systems that are sets of operations and related activities. Control of all systems helps to ensure the establishment will produce safe and effective drugs that meet the identity, strength, quality, and purity characteristics as intended.

Risk-based inspections of manufacturing sites (includes repackaging, contract labs, etc.) conducted under this program:

- 1) reduce the risk of adulterated drugs reaching the marketplace;
- 2) provide for timely evaluation of new manufacturing operations in establishments; and,

- 3) provide for regular feedback from the Agency to individual establishments on the continuing status of CGMP compliance.

FDA's approach to inspections and compliance for manufactured animal drugs balances risks and resources. To facilitate this, CP 7371.001 establishes a systems-based approach to CGMP inspections. Inspectional coverage of specific drugs and systems allows FDA to determine an appropriate profile status for each class of drug manufactured by a firm, and to determine the overall final classification of the establishment. These profile statuses and final inspection classifications can be used for future decisions related to drug approval, export certificate issuance, etc.

This animal drug manufacturing CP provides broad coverage appropriate to inform a variety of regulatory decisions. By contrast, the Pre-Approval Inspections Compliance Program 7368.001 directs focus on specific application issues.

The CGMP inspection is defined as audit coverage of 4 or more systems ([Full Inspection](#)), or 2 or more systems ([Abbreviated Inspection](#)), with mandatory coverage of the Quality System (see [A Scheme of Systems for the Manufacture of Drugs/Drug Products](#) below). Inspection options include coverage of different numbers of systems depending on the purpose of the inspection. Inspecting the minimum number of systems or more systems, as deemed necessary by the ORA Division, will provide the basis for an overall CGMP compliance decision.

1. Inspection of Systems

Inspections of drug establishments should be conducted and reported using the systems approach, which increases efficiency when conducting inspections and facilitates evaluation of multiple [profile classes](#). This systems approach requires detailed inspection documentation, including observations, specific examples (system components, products and profiles) and discussions. Outcomes from the systems-based inspection reflects the state of control in that system for every profile class.

One risk-based systems inspection will generally result in a determination of acceptability/non-acceptability for all profile classes for the establishment. If a particular system is adequate, it should be adequate for all profile classes for the establishment. For example, the way an establishment handles "materials" (i.e., receipt, sampling, testing, acceptance, etc.) for one profile class is ordinarily the same for other profile classes. The Investigator should not have to inspect the Material System for each profile class. Likewise, in the Production System, there are general requirements like SOP use, charge-in of components, equipment identification, in-process sampling and testing which can be evaluated through selection of example products in various profile classes. However, under each system, there may be certain unique procedures/processes for particular profile class(s). For example, if a firm manufactures both sterile and non-sterile drugs and produces Water for Injection USP for use only in sterile products (covered as part of the Materials System),

this process applies only to profile codes applicable to sterile drugs. Selecting unique functions within a system will be at the discretion of the lead Investigator. Any given inspection need not cover every system. See [Part III, Section B – Inspectional Approaches](#).

Complete inspection of one system may necessitate further follow up within another system to fully document the findings. However, this coverage does not constitute nor require complete coverage of the other systems.

A Scheme of Systems for the Manufacture of Drugs/Drug Products

A general scheme of systems for auditing the manufacture of drugs and drug products consists of the following:

1. Quality System: This system assures overall compliance with CGMP and internal procedures and specifications. The system includes the quality control unit and all its review and approval duties (e.g., change control, reprocessing, batch release, annual record review, validation protocols, and reports, etc.). This system includes evaluations of all product defects, complaints, and returned and salvaged drug products. See the CGMP regulation, 21 CFR 211 Subparts B, E, F, G, I, J, and K.
2. Facilities and Equipment System: This system includes the measures and activities which provide an appropriate physical environment and resources used in the production of the drugs or drug products. It includes:
 - a) Buildings and facilities along with maintenance;
 - b) Equipment qualifications (installation and operation); equipment calibration and preventative maintenance; and cleaning and validation of cleaning processes as appropriate. Process performance qualification will be evaluated as part of the inspection of the overall process validation which is done within the system where the process is employed; and,
 - c) Utilities that are not intended to be incorporated into the product such as heating, ventilating, and air-conditioning (HVAC), compressed gases, steam, and water systems.

See the CGMP regulation, 21 CFR 211 Subparts B, C, D, and J.

3. Materials System: This system includes measures and activities to control finished products, components, including water or gases that are incorporated into the product, containers, and closures. It includes validation of computerized inventory control processes, drug storage, distribution controls, and records. See the CGMP regulation, 21 CFR 211 Subparts B, E, H, and J.

4. Production System: This system includes measures and activities to control the manufacture of drugs and drug products including batch compounding, dosage form production, in-process sampling and testing, and process validation. It also includes establishing, following, and documenting performance of approved manufacturing procedures. See the CGMP regulation, 21 CFR 211 Subparts B, F, and J.

5. Packaging and Labeling System: This system includes measures and activities that control the packaging and labeling of drugs and drug products. It includes written procedures, label examination and usage, label storage and issuance, label reconciliation, packaging and labeling operations controls, and validation of these operations. See the CGMP regulation, 21 CFR 211 Subparts B, G, and J.

6. Laboratory Control System: This system includes measures and activities related to laboratory procedures, testing, analytical methodology development and validation or verification, and the stability program. See the CGMP regulation, 21 CFR 211 Subparts B, I, J, and K.

The organization and personnel, including appropriate qualifications and training, employed in any given system, will be evaluated as part of that system's operation. See the CGMP regulation, 21 CFR 211 Subpart B. Production, control, or distribution records required to be maintained by the CGMP regulation and selected for review should be included for inspection audit within the context of each of the above systems. See the CGMP regulation, 21 CFR 211 Subpart J. Inspections of contract companies should be within the system for which the product or service is contracted as well as their Quality System.

2.3 – PROGRAM MANAGEMENT INSTRUCTIONS

B. Definitions

1. Inspection Option (Full/Abbreviated)

The Full Inspection Option

The Full Inspection Option is a surveillance or compliance inspection which is meant to provide a broad and deep evaluation of the establishment's CGMP status. See Part III, [Selecting the Full Inspection Option](#) for information on when to select the Full Inspection Option.

The Full Inspection Option will normally include an inspection audit of at least four of the systems, one of which must be the Quality System.

The Abbreviated Inspection Option

The Abbreviated Inspection Option is a surveillance or compliance inspection which is meant to provide an efficient update evaluation of an establishment's compliance with CGMP. Generally, this will be done when an establishment has a record of satisfactory CGMP compliance, with no significant recalls, or product defect or alert incidents, or with little shift in the manufacturing profiles of the establishment within the previous two years. See Part III, [Selecting the Abbreviated Inspection Option](#) for the conditions when the Abbreviated Inspection option is appropriate.

The Abbreviated Inspection Option will normally include an inspection audit of at least two of the systems, one of which must be the Quality System.

2. Surveillance Inspections

Surveillance inspections are inspections conducted as a routine assignment with no other indicators of non-compliance.

3. 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 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 certain "for-cause" inspections, which are compliance inspections 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 defective products, or by other means. These issues may be covered under other compliance programs or by a limited assignment memorandum; however, when inspectional coverage meets the requirements for a Full or Abbreviated CGMP inspection, it is to be reported under this program. For-cause inspections may be assigned under this program as the need arises.

4. 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 finished drug products for which there is an adequate level of assurance of quality, strength, identity, and purity.

An establishment is out of control if any one system is out of control. A system is out of control if the quality, identity, strength, and purity of the products resulting from that system(s) fail to comply with CGMP. Documented CGMP deficiencies provide the evidentiary support for establishing and concluding that a system is not operating in a state of control. See [Part V – Regulatory/Administrative Strategy](#) for a discussion of compliance actions based on inspection findings demonstrating out of control establishment systems.

5. *Drug Process*

A drug process is a related series of operations which result in the preparation of a drug or drug product. Major operations or steps in a drug process may include mixing, granulation, encapsulation, tableting, chemical synthesis, fermentation, aseptic filling, sterilization, packing, labeling, testing, etc.

C. **Inspection Frequency/Depth**

The Field will conduct drug manufacturing inspections and maintain profiles which will ensure that each drug establishment receives risk-based inspectional coverage, as provided for in the [STRATEGY](#) section.

6. *Surveillance Inspection Frequency / Depth*

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 finding pertaining to that system are ordinarily considered applicable to all products which use it. Investigators should select a suitable number and type of products to inspect to accomplish adequate coverage of the system. Selection of products should be made so that coverage is representative of the establishments' overall abilities in complying with CGMP requirements.

The frequency of assigned surveillance inspections is determined by CVM based on anticipated field resources, statutory obligations, regulatory requirements, the establishment's compliance history, the technology employed, and the characteristics of the products. 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. CVM will separately identify foreign firms for surveillance coverage and will notify ORA.

Inspections for this compliance program may be performed during visits to a firm when

operations are being evaluated according to other compliance programs, such as CDER's CPGM 7356.002 – Drug Manufacturing Inspections for all human drug products, or other investigations.

7. Compliance Inspection Frequency / Depth

Domestic Firms: CVM will request the ORA Division initiate a “for-cause” compliance inspection when appropriate. The ORA Program Division can conduct a for-cause inspection on its own initiative (e.g. in response to a FAR, or based on information obtained from another center), but should notify CVM 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 inspection assignments. After taking the regulatory action, the ORA Division should contact CVM to confirm that CVM does not intend to issue a special follow-up assignment memorandum.

The ORA Division is responsible for assigning and conducting all mandated compliance follow-up inspections (e.g. injunction monitoring).

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

D. Selecting Systems, Processes, and Products for Coverage

The selection of the system(s) for coverage will be made by the ORA Division based on such factors as a given establishment's specific operation, history of previous coverage, history of compliance, or other priorities determined by the ORA Division.

The ORA Division should give preferential coverage to significant drug processes, which are those that utilize the systems in the establishment broadly and/or which contain steps with unique or difficult manipulation in the performance of a step.

Products posing special manufacturing features, e.g., low dose products, narrow therapeutic range drugs, combination drugs, modified release products, etc., and new products made under an approved NADA/ANADA, should be given increased consideration when selecting products for coverage. Coverage decisions should consider the potential regulatory significance of any CGMP deviations that might be found. This significance depends, in part, on the overall risk of the products. Product-specific risk for veterinary drugs includes:

- whether the product must be sterile;
- whether the product is used in food-producing animals (especially drugs with the

potential to cause a drug residue in food-producing animals due to inconsistent potency or superpotency):

- potential to increase development of antimicrobial resistance (e.g., sub-potent antimicrobial);
- products marketed for use in one of the major species (cattle, horses, swine, chickens, turkeys, dogs and cats); and
- health hazards to humans handling/administering the drug caused by improper CGMP controls (e.g., container integrity of potent drugs, euthanasia drugs, etc.).

Products intended *solely* to cleanse or beautify animals, are commonly referred to as “grooming aids.” Products such as animal grooming aids without drug claims in their labeling should receive the *lowest* priority coverage. Do not cite CGMP violations for grooming aids unless you have reason to believe they are drugs. See Compliance Policy Guide 653.100, Animal Grooming Aids, for more information.

E. Profiling

Firm profiles provide the compliance status as well as an inventory of product categories covered during a CGMP inspection. The inspection findings will be used as the basis for updating all profile classes via eNSpect. Normally, an inspection under the systems approach will result in all profile classes being updated. If all profile classes cannot be covered by evaluating only two systems, then an effort should be made to expand the inspectional coverage of the establishment’s processing to gather enough information to update all profile classes. But if all profile classes cannot be updated, the EIR should note the reason for not updating all the profile classes.

PART III - INSPECTIONAL**3.1 – OPERATIONS****A. Applicable Standards**

Review and use the Current Good Manufacturing Practices for Finished Pharmaceuticals regulation (21 CFR Part 211) to evaluate manufacturing processes for drug products. Use the statutory CGMP standard, FDCA § 501(a)(2)(B), to evaluate the manufacturing processes for all other drugs, including APIs.

The investigator should conduct inspections according to the [STRATEGY](#) section found in Part II of this compliance program. Recognizing that drug establishments vary greatly in size and scope, and manufacturing systems are sophisticated, the approach to inspecting each establishment should be carefully planned. For example, it may be more appropriate to review the Quality System thoroughly before entering production areas in some establishments; in others, the Quality System review could take place concurrently with inspection of another system or systems selected for coverage. The complexity and variability necessitate a flexible inspection approach; one which allows the Investigator to choose the inspection focus and depth appropriate for a specific establishment.

1. Inspection of Finished Dosage Forms

Inspectional Observations noting CGMP deficiencies should be related to a statutory requirement and/or regulation. Requirements for the manufacture of drug products (i.e. finished dosage forms) are in the CGMP regulation (21 CFR Part 211). The Compliance Policy Guides and other guidance documents assist in the proper interpretation and application of CGMP. The CGMP regulations apply to the manufacture of all drug products, regardless of whether the drug is prescription, OTC, approved, or unapproved. The CGMP regulation also applies to drug products used in clinical trials.

2. Inspection of APIs

The CGMP regulation in Part 211 does not establish legal requirements applicable to the manufacture of Active Pharmaceutical Ingredients (APIs). However, the Act's statutory requirement to follow "current good manufacturing practice to assure that such drug meets the requirements of this chapter as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess" applies to all drugs, including APIs. (See FDCA § 501(a)(2)(B)). During the promulgation of the CGMP regulation, FDA stated that while the "CGMP regulations are not applied to the manufacture of bulk drug components, there are numerous instances where good manufacturing practices for bulk drug components would parallel the requirements set forth

in Part 211. For this reason, FDA will utilize the standards of Part 211 as guidelines during inspections of manufacturers of bulk drug components....” (43 FR 45014, 45026). FDA has not published superseding guidance on the manufacturing of animal drug APIs; therefore, while the CGMP regulations in Part 211 should not be referenced as the basis for a CGMP deficiency in the manufacture of APIs, they are conceptual guidance for CGMP in animal drug API manufacturing. FDA has published the Q7 ICH guidance document that provides general guidance regarding CGMP for human API manufacturers. While the scope of the Q7 ICH document is currently limited to human drug products, it may be used as a guideline in describing the deficiencies observed. Note that drug products (i.e. finished dosage forms) may be easily mistaken for APIs when stored in bulk containers (especially when the finished dosage form is a powder or liquid), but all manufacturing of drug products is subject to the requirements of 21 CFR Parts 210 and 211.

3. Use of Guidance Documents

Guidance documents do not establish legal requirements. They state examples of ways to meet requirements. Guidance documents may not be used as the justification for an inspectional observation. Rather, the justification for an observation must be that the objectionable condition cited is not in conformance with CGMP or other statutory requirements. Guidance documents, such as FDA’s Guidance for Industry documents may provide interpretations of requirements, which may assist in the evaluation of CGMP. Although guidance documents are not binding on FDA or industry, “they represent the agency’s current thinking. FDA employees may depart from guidance documents only with appropriate justification and supervisory concurrence.” (21 CFR 10.115(d)(3)). Therefore, if a firm’s practices are consistent with a guidance, and this guidance is applicable to the firm’s operations, you may not include them on an FDA 483 without supervisory concurrence and justification.

4. Inspectional Observations

The FDA 483 should be specific and contain only factual observations of significant items ranked in order of significance. When possible, repeated or similar observations should be consolidated. Refrain from making conclusions. Do not use the term "inadequate" without explaining why and how. Do not quote regulations (i.e. specific 21 CFR sections) when listing deficiencies. Refer to the Investigations Operations Manual (IOM) for further guidance on the content of Inspectional Observations.

B. Inspection Approaches

This program provides two surveillance inspectional options, Abbreviated Inspection Option and Full Inspection Option. See the [Surveillance Inspections](#) in Part II of this program.

1. Selecting the Full Inspection Option

The Full Inspection Option will include inspection of at least four of the systems as listed under the [STRATEGY](#) section in Part II, one of which must be the Quality System.

- a. Select the Full Inspection Option for the initial FDA inspection of a facility.
- b. Select the Full Inspection Option when the establishment has a history of fluctuating into and out of compliance. To determine if the establishment meets this criterion, the ORA Division should utilize all information at their disposal, such as, inspection results, results of sample analyses, complaints, Three-day NADA/ANADA Field Alert Reports, recalls, and previous compliance actions.
- c. Evaluate high risk changes by comparing current operations against the EIR for the previous Full Inspection of the establishment. The following types of changes are typical of those that warrant the Full Inspection Option:
 - (1) Potential for cross-contamination (processes, products, product lines)

The Full Inspection Option must be used after the initial introduction of any new class of products that poses special cross-contamination risks (e.g., hormones, other highly potent drugs, cytotoxic drugs, potentially sensitizing drugs, etc.) with mandatory coverage of the Facilities and Equipment System and the Materials System.
 - (2) Technology/facility improvements (knowledge gaps, impact of construction on products manufactured during or immediately after major renovation)
- d. Full Surveillance Inspection Option is mandatory for follow up inspections after OAI classifications, including a Warning Letter, an Import Alert, a regulatory meeting, or other significant regulatory action.
- e. A Full Inspection may also be conducted on a surveillance basis, at the Division's discretion. The Full Inspection Option will satisfy the risk-based inspection requirement.

2. Selecting the Abbreviated Inspection Option

The Abbreviated Inspection Option includes inspection of at least two of the above systems, one of which must be the Quality System. During the course of an abbreviated inspection, verification of quality system activities may require limited coverage in other systems. The Investigator should ensure that the optional systems are rotated in successive Abbreviated Inspections. Some establishments participate in a limited part of the production of a drug or drug product, e.g., a contract laboratory. Such establishments

may employ only two of the systems defined. In these cases, the inspection of the two systems will comprise inspection of the entire establishment and will therefore be considered a Full Inspection.

An Abbreviated Inspection should convert to a Full Inspection based on findings of significant objectionable conditions in one or more systems.

This abbreviated inspection option involves CGMP surveillance over establishments, including establishment activities, conditions and practices. It is intended for CPGM 7371.001 coverage of establishments previously inspected and classified No Action Indicated (NAI) or Voluntary Action Indicated (VAI) for products and acceptable for profiles.

An abbreviated inspection is adequate for routine coverage and will satisfy the risk-based inspectional requirement.

It is not anticipated that Full Inspections will be conducted every inspection. They may be conducted at less frequent intervals, perhaps at every third or fourth inspection cycle. Divisions should consider selecting different optional systems for inspection coverage as a cycle of Abbreviated Inspections are carried out to maintain comprehensive information on the establishment's overall manufacturing activities.

C. Systems-based Inspection Coverage

1. Quality System

Assessment of the Quality System is conducted in two phases. The first phase is to evaluate whether the Quality Control Unit has fulfilled its responsibility to review and approve all procedures related to production, quality control, and quality assurance and assure the procedures are adequate for their intended use. This also includes the associated recordkeeping systems. The second phase is to assess the data collected to identify quality problems which may link to other major systems for inspectional coverage.

For each of the following, the establishment should have written and approved procedures and documentation. The establishment's adherence to written procedures should be verified through observation whenever possible. These areas are not limited only to finished products but may also incorporate starting materials and in-process materials. Deficiencies observed in Quality System likely exist in other major systems, which would warrant expansion of coverage. CPGM 7371.001 requires coverage of all areas under this system. The depth of coverage may vary depending upon risk and inspectional findings.

- Batch production and control record review and approval prior to distribution of batches.
- Product reviews: at least annually; should include information from areas listed

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below as appropriate; batches reviewed, for each product, are representative of all batches manufactured; trends are identified; refer to 21 CFR 211.180(e) and 21 CFR 514.

- Discrepancy and failure investigations related to manufacturing and testing: documented; evaluated; investigated in a timely manner; includes corrective action where appropriate.
- Change Control: documented; evaluated; approved; need for revalidation assessed.
- Product Improvement Projects: for marketed products; for cross contamination (beta-lactams).
- Reprocess/Rework: evaluation, review and approval; impact on validation and stability.
- Returns/Salvages: assessment; investigation expanded where warranted; disposition.
- Rejects: investigation expanded where warranted; corrective action where appropriate.
- Stability Failures: investigation expanded where warranted; need for field alerts evaluated; disposition.
- Quarantine products.
- Validation: status of required validation/revalidation (e.g., computer, manufacturing process, laboratory methods).
- Training/qualification of employees in quality control unit functions.
- Complaint reviews (quality): documented; evaluated; investigated in a timely manner; includes corrective action where appropriate.
- 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 followed; refer to 21 CFR 211 and 21 CFR 514.
- Check the complaint files to see whether there are any ADE complaints not submitted to CVM via FDA Form 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 FDA Form 1932. Review that follow-up actions are 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. Further investigation of the batch records may be considered when there are repeated reports of the same type of defect.

2. Facilities and Equipment System

For each of the following, the establishment should have written and approved procedures and documentation. The establishment's adherence to written procedures should be verified through observation whenever possible. Deficiencies in this system likely exist in other systems, which would warrant expansion of coverage. When this system is selected for coverage in addition to the Quality System, CPGM requires coverage of all Facilities and Equipment System areas, as listed below; however, the depth of coverage may vary depending upon risk and inspectional findings.

Cross-contamination is a significant concern in a facility that manufactures more than one product. The firm's method for separating the products, either by space or time, should be reviewed to ensure there is no potential for cross-contamination. If equipment is not dedicated to one product, records of cleaning and cleaning validation should be reviewed. If personnel work in more than one area, the employees should be 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. Related regulations for finished pharmaceuticals: 21 CFR 211.42–211.67 require facility and equipment controls to prevent contamination and to ensure well-organized operations.

Although 211.42(d) and 211.46(d) only apply to human drugs, cross-contamination of animal drugs is not acceptable and the facility should have safeguards in place to prevent any cross-contamination.

Facilities

- cleaning and maintenance
- facility layout and air handling systems for prevention of cross-contamination (e.g. penicillin, beta-lactams, steroids, hormones, cytotoxics, etc.)
- specifically designed areas for the manufacturing operations performed by the establishment to prevent contamination or mix-ups
- general air handling systems

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- control system for implementing changes in the building
- lighting, potable water, washing and toilet facilities, sewage and refuse disposal
- sanitation/disinfection of the building, use of rodenticides, fungicides, insecticides, cleaning and sanitizing/disinfecting agents
- appropriate aseptic processing facilities, including easily cleanable surfaces; temperature and humidity controls; air supplied through HEPA filters; environmental monitoring program, cleaning, disinfection and maintenance of facilities and equipment used to control aseptic conditions.

Equipment

- equipment cleaning, maintenance and use logs when required
- equipment installation and operational qualification where appropriate
- adequacy of equipment design, size, and location
- equipment surfaces; not reactive, additive, or absorptive
- appropriate use of equipment operations substances, (lubricants, coolants, refrigerants, etc.) contacting products/containers/etc.
- cleaning procedures and cleaning validation
- controls to prevent contamination, particularly with any pesticides or any other toxic materials, or other drug or non-drug chemicals including beta-lactam
- qualification, calibration and maintenance of storage equipment, such as refrigerators and freezers for ensuring that standards, raw materials, reagents, etc. are stored at the proper temperatures
- equipment qualification, calibration and maintenance, including computer qualification/validation and security
- control system for implementing changes in the equipment
- equipment identification practices
- documented investigation into any unexpected discrepancy

3. Materials System

For each of the following, the establishment should have written and approved procedures and documentation. The establishment's adherence to written procedures should be verified through observation whenever possible. These areas are not limited only to finished products and may also incorporate starting materials and in-process materials. These areas may indicate deficiencies not only in this system but also in other systems that would warrant expansion of coverage. When this system is selected for coverage in addition to the Quality System, all areas of the Materials System listed below should be covered; however, the depth of coverage may vary depending upon inspectional findings.

- training/qualification of personnel
- identification of components, containers, closures
- inventory of components, containers, closures
- storage conditions
- storage under quarantine until tested or examined and released
- representative samples collected, tested or examined using appropriate means
- at least one specific identity test is conducted on each lot of each component
- a visual identification is conducted on each lot of containers and closures
- testing or validation of supplier's test results for components, containers and closures
- rejection of any component, container, closure not meeting acceptance requirements. Investigate fully the establishment's procedures for verification of the source of components
- appropriate retesting/reexamination of components, containers, closures
- first in-first out use of components, containers, closures as appropriate
- quarantine of rejected materials
- water and process gas supply, design, maintenance, validation and operation
- containers and closures should not be additive, reactive, or absorptive to the drug product

- control system for implementing changes in the materials handling operations
- qualification/validation and security of computerized or automated data handling system
- finished product distribution records by lot
- documented investigation into any unexpected discrepancy

4. Production System

For each of the following, the establishment should have written and approved procedures and documentation. The establishment's adherence to written procedures should be verified through observation whenever possible. These areas are not limited only to finished product and may also incorporate starting materials and in-process materials. These areas may indicate deficiencies not only in this system but also in other systems that would warrant expansion of coverage. When this system is selected for coverage in addition to the Quality System, all areas of the Productions System listed below should be covered; however, the depth of coverage may vary depending upon inspectional findings.

- training/qualification of personnel
- control system for implementing changes in processes
- adequate procedure and practice for charge-in of components
- identification of equipment with contents, and where appropriate phase of manufacturing and/or status
- validation and verification of cleaning/sterilization/depyrogenation of containers and closures
- calculation and documentation of actual yields and percentage of theoretical yields
- contemporaneous and complete batch production documentation
- established time limits for completion of phases of production
- implementation and documentation of in-process controls, tests, and examinations (e.g. pH, adequacy of mix, weight variation, clarity)
- justification and consistency of in-process specifications and drug product final specifications

- prevention of microbiological contamination of drug products purporting to be sterile, including the validation of any sterilization process
- prevention of objectionable microorganisms in non-sterile drug products
- adherence to preprocessing procedures (e.g., set-up, line clearance, etc.)
- equipment cleaning, maintenance and use logs
- master production and control records
- batch production and control records
- process validation, including validation and security of computerized or automated data handling system
- change control; the need for revalidation evaluated
- documented investigation into any unexpected discrepancy

5. Packaging and Labeling System

For each of the following, the establishment should have written and approved procedures and documentation. The establishment's adherence to written procedures should be verified through observation whenever possible. These areas are not limited only to finished products and may also incorporate starting materials and in-process materials. These areas may indicate deficiencies not only in this system but also in other systems that would warrant expansion of coverage. When this system is selected for coverage in addition to the Quality System, all Packaging and Labeling System areas listed below should be covered; however, the depth of coverage may vary depending upon inspectional findings.

- training/qualification of personnel
- acceptance operations for packaging and labeling materials
- control system for implementing changes in packaging and labeling operations
- adequate storage for labels and labeling, both approved and returned after issued
- control of labels which are similar in size, shape, and color for different products
- finished product cut labels for immediate containers which are similar in appearance without some type of 100 percent electronic or visual verification system or the use of dedicated lines

- gang printing of labels is not done, unless these are differentiated by size, shape, or color
- control of filled unlabeled containers that are later labeled under multiple private labels
- adequate packaging records that will include specimens of all labels used
- control of issuance of labeling, examination of issued labels and reconciliation of used labels
- examination of the labeled finished product
- adequate inspection (proofing) of incoming labeling
- use of lot numbers, destruction of excess labeling bearing lot/control numbers
- physical/spatial separation between different labeling and packaging lines
- monitoring of printing devices associated with manufacturing lines
- line clearance, inspection and documentation
- adequate expiration dates on the label
- validation of packaging and labeling operations including validation and security of computerized or automated data handling system
- documented investigation into any unexpected discrepancy

6. Laboratory Control System

For each of the following, the establishment should have written and approved procedures and documentation. The establishment's adherence to written procedures should be verified through observation whenever possible. These areas are not limited only to finished product and may also incorporate starting materials and in-process materials. These areas may indicate deficiencies not only in this system but also in other systems that would warrant expansion of coverage. When this system is selected for coverage in addition to the Quality System, all Laboratory Control System areas listed below should be covered; however, the depth of coverage may vary depending upon inspectional findings.

- training/qualification of personnel

- adequacy of staffing for laboratory operations
- adequacy of equipment and facility for intended use
- calibration and maintenance programs for analytical instruments and equipment
- validation and security of computerized or automated data handling system
- reference standards; source, purity and assay, and tests to establish equivalency to current official reference standards as appropriate
- system suitability checks on chromatographic systems (e.g., GC or HPLC)
- specifications, standards, and representative sampling plans
- adherence to the written methods of analysis
- validation/verification of analytical methods
- control system for implementing changes in laboratory operations
- required testing is performed on the correct samples
- documented investigation into any unexpected discrepancy
- complete analytical records from all tests and summaries of results
- quality and retention of raw data (e.g., chromatograms and spectra)
- correlation of result summaries to raw data; presence of unused data
- adherence to an adequate Out of Specification (OOS) procedure which includes timely completion of the investigation
- adequate reserve samples; documentation of reserve sample examination
- stability testing program, including demonstration of stability indicating capability of the test methods

D. Special Topics

1. 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.³Firms 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.

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 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)
- Records, reports, or information referring to failing biostudies.
- Discrepancies (e.g., color, shape, embossing) between material used in a biostudy and

³ Guidance for Industry - Data Integrity and Compliance With Drug CGMP Questions and Answers Guidance for Industry

reserve samples.

- 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.

2. *Inspection of Sterile Drug Manufacturers*

There are two broad methods to produce a sterile drug product:

- Terminal Sterilization
- Aseptic Processing of sterilized unit components

There are basic differences between the production of sterile drug products using aseptic processing and production using terminal sterilization. Terminal sterilization should be utilized when the product and container/closure system are able to withstand the terminal sterilization process.

Terminal Sterilization

The terminal sterilization process usually involves filling and sealing product containers under high quality environmental conditions designed to minimize microbial and particulate contamination of the product. This minimization of upstream bioburden reduces the challenge to the subsequent sterilization process. In most cases, the product, container, and closure have low bioburden, but are not sterile at the time of filling. The product is then subjected to a sterilization process in its final container.

There are various methods of terminal sterilization including:

- Moist Heat and Dry Heat Sterilization
- Irradiation
- Ethylene Oxide (typically for assembled components/kits)

Types of sterilization cycles include:

Overkill method:

- Generally used for heat stable materials.
- Designed to provide a significant level of sterility assurance regardless of the number and resistance of the actual bioburden organisms in the load.
- Results in greater heat/exposure input to the product or items being sterilized.

Bioburden Based cycle:

- Requires studies to determine the number and resistance of the microorganisms found in the product and the bioburden load of the incoming components and containers/closures.
- Cycle development to destroy the microbial load, but not degrade the product.
- Routine bioburden monitoring of batches and ongoing knowledge of the heat/exposure resistance of organisms found in product bioburden, container/closure bioburden and environmental monitoring samples.

Aseptic Processing

Aseptic processing presents a higher risk of microbial contamination of the product than terminal sterilization. In an aseptic filling process, the drug product, containers and closures are sterilized separately and then brought together under an extremely high-quality environmental condition designed to reduce the possibility of a non-sterile unit. Aseptic processing involves more variables than terminal sterilization. Any manual or mechanical manipulation of the sterilized drug, containers, or closures prior to or during aseptic filling and assembly poses the risk of microbial contamination.

Some types of aseptic processing involve manual manipulations of sterile components, containers, and closures in addition to routine operator interventions in the critical area. Humans are a significant source of contamination in traditional aseptic processing, especially in production lines that require operators to routinely enter critical areas (ISO 5, or Grade A) of the filling line. Aseptic processing systems based on more advanced control-based technologies, such as Restricted Access Barrier Systems (RABS) and Blow-Fill-Seal systems, are designed to reduce human interventions in the critical areas of the fill line while an Isolator System completely separates the aseptic filling line from the external environment and minimizes employee interaction with the critical area.

When conducting inspections of sterile drug manufacturers, it is important to cover systems and areas within systems that present the greatest risk of product contamination and/or require strict control of processing parameters. For example, if a firm has several aseptic processing lines, cover the line(s) that require the most manual manipulations in the ISO 5 areas. If the firm terminally sterilizes a number of products, review one that is sensitive to heat and requires a product specific (bioburden based) sterilization cycle. Note: For terminal sterilized products that are aseptically filled prior to terminal sterilization, less rigorous aseptic controls can be considered.

E. 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.

F. 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 therapeutic range, wide range of toxicity, or a low dosage strength. Include samples of products of minimal therapeutic significance only when they illustrate highly significant CGMP deficiencies.

G. 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).

H. 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. Identify and explain in the body of the report the rationale for inspecting the profile classes covered. Report and discuss in full any adverse findings by systems under separate captions. Add additional information as needed or desired, for example, a description of any significant changes that have occurred since previous inspections.

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

PART IV - ANALYTICAL

A. Analyzing Laboratories

Contact ORSOMPSLOProgramCoordinators@fda.hhs.gov for servicing laboratories for all chemical and microbiological testing. When contacting ORS/OMPTSLO 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.]

B. 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

C. Methodology

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

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 management is unwilling or unable to voluntarily correct violations. However, FDA may take immediate action without prior notice in circumstance outlined in the Regulatory Procedures Manual (RPM), section 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 Compliance (HFV-233) 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. Additionally, if one profile class fails, all profile classes affected by the same system(s) deficiencies fail. Until an establishment is in compliance, any pending or future NADA/ANADA(s) affected by the system(s) failure may not be approved.

The therapeutic significance of the drug 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 Compliance (HFV-233) for guidance in developing the compliance strategy. Determining the most effective and efficient way to protect animals and the consuming public must be 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. Individuals and companies who violate the FD&C Act with intent to defraud or those deemed appropriate under the factors described in RPM section 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 samples or laboratory testing is necessary for CGMP adulteration charges.

A. Significant Failures – CGMP Systems

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 include, but are not limited to, the following:

Quality System

- 1) Pattern of failure to review/approve procedures.
- 2) Pattern of failure to document execution of operations as required.
- 3) Pattern of failure to review documentation.
- 4) Pattern of failure to conduct investigations and resolve discrepancies/failures/deviations/complaints.
- 5) Pattern of failure to assess other systems to assure compliance with CGMP and SOPs.

Facilities and Equipment

- 1) Contamination with filth, objectionable microorganisms, toxic chemicals or other drug chemicals, or a reasonable potential for contamination, with demonstrated avenues of contamination, such as airborne or through unclean equipment.
- 2) Pattern of failure to validate cleaning procedures for non-dedicated equipment. Lack of demonstration of effectiveness of cleaning for dedicated equipment.
- 3) Pattern of failure to document investigation of discrepancies.
- 4) Pattern of failure to establish/follow a control system for implementing changes in the equipment.
- 5) Pattern of failure to qualify production manufacturing equipment and equipment used for

the manufacture of support utilities (e.g., Water Systems, HVAC, gases) and QC laboratory equipment, including computers.

Materials System

- 1) Release of materials for use or distribution that do not conform to established specifications.
- 2) Pattern of failure to conduct one specific identity test for components.
- 3) Pattern of failure to document investigation of discrepancies.
- 4) Pattern of failure to establish/follow a control system for implementing changes in the materials handling operations.
- 5) Lack of validation of water systems as required depending upon the dosage form.
- 6) Lack of validation of computerized systems.

Production System

- 1) Pattern of failure to establish/follow a control system for implementing changes in the production system operations.
- 2) Pattern of failure to document investigation of discrepancies.
- 3) Lack of process validation.
- 4) Lack of validation of computerized systems.
- 5) Pattern of incomplete or missing batch production records.
- 6) Pattern of nonconformance to established in-process controls, tests, and/or specifications.

Packaging and Labeling

- 1) Pattern of failure to establish/follow a control system for implementing changes in the packaging and/or labeling operations.
- 2) Pattern of failure to document investigation of discrepancies.
- 3) Lack of validation of computerized systems.
- 4) Lack of control of packaging and labeling operations that may introduce a potential for mislabeling.

- 5) Lack of packaging validation.

Laboratory Control System

- 1) Pattern of failure to establish/follow a control system for implementing changes in the laboratory operations.
- 2) Pattern of failure to document investigation of discrepancies.
- 3) Lack of validation of computerized systems and/or automated data collection systems.
- 4) Pattern of inadequate sampling practices.
- 5) Lack of validated analytical methodologies.
- 6) Pattern of failure to follow approved analytical procedures.
- 7) Pattern of failure to follow an adequate OOS procedure.
- 8) Pattern of failure to retain raw data.
- 9) Lack of stability indicating methods.
- 10) Pattern of failure to follow the stability programs.

B. Deficiencies Related to APIs

In a recommendation for regulatory action for API CGMP deficiencies, cite the statute (Section 501(a)(2)(B)). The recommendation should not cite the finished pharmaceutical regulations in Part 211 or ICH Q7 as the legal basis for the violation. ICH Q7 may be used as a guideline in describing the deficiencies observed. Any regulatory action based upon CGMP noncompliance for APIs should demonstrate how the observed deviations could or did result in actual or potential defects or risk to contamination. In evaluating whether to recommend regulatory or administrative action, consider the critical attributes of the API, its therapeutic significance, and its intended use in finished drug product manufacturing. In evaluating whether to recommend regulatory or administrative action, consider the critical attributes of the API, its therapeutic significance, and its intended use in finished drug product manufacturing.

Evidence that supports a significant deficiency or pattern of deficiencies within a system may demonstrate the failure of a system. A failure of a system puts all drugs at risk and is to be promptly corrected. The following lists the deficiencies that should result in a recommendation for regulatory action to CVM; other deficiencies may also warrant regulatory action:

- 1) Contamination of APIs with filth, objectionable microorganisms, toxic chemicals, or

significant amounts of other types of chemicals, or a reasonable potential for such contamination because of a finding of a demonstrated route of contamination. (Facilities and Equipment System; Production System)

- 2) Failure to show that API batches conform to established specifications, such as NADA requirements, USP/NF, customer specifications, and label claims. (Quality System)
- 3) Failure to comply with commitments in drug applications, including DMFs and VMF's, which should be accurate and current with respect to all required information, such as manufacturing process, impurity profiles (if filed), and other specifications or procedures associated with the manufacture of the API. (Quality System)
- 4) Distribution of an API that does not conform to established specifications. (Quality System)
- 5) Deliberate blending of API batches to dilute or hide filth or other noxious contaminants or blending to disguise a critical quality defect in an attempt to obtain a batch that meets its specifications. (Production System)
- 6) Failure to demonstrate that water, including validation of the process water purification system, and any other solvents used in the final step of the API process are chemically and microbiologically suitable for their intended use and does not adversely alter the quality of the API. (Materials System)
- 7) Lack of adequate validation of critical steps in the API process, particularly concerning final separation and purification of the API, or when there is evidence that an API process is not adequately controlled. Lack of adequate control may be indicated by repeated batch failures or wide variation in final yields as compared to process average over time. (Quality System; Production System)
- 8) Implementation of retrospective process validation for an existing API process when the process has changed significantly, when the firm lacks impurity profile data, or when there is evidence of repeated batch failures due to process variability. (Quality System; Production System)
- 9) Failure to establish an impurity profile for each API process. FDA expects manufactures to establish complete impurity profiles for each API as part of the process validation effort. This includes collecting data on (1) actual and potential organic impurities that may arise during synthesis, purification, and storage of the API; (2) inorganic impurities that may derive from the API process; and (3) organic and inorganic solvents used during the manufacturing process that are known to carry over to the API. Impurity profile testing of each batch or after a specified number of batches may detect new impurities that may appear because of a deliberate or nondeliberate change in the API manufacturing process. (Laboratory Control System)

- 10) Failure to show that a reprocessed batch complies with all established standards, specifications, and characteristics. (Quality System; Laboratory Control System)
- 11) Failure to test for residues of organic/inorganic solvents used during manufacturing that may carry over to the API using analytical procedures with appropriate levels of sensitivity. (Laboratory Control System)
- 12) Failure to have a formal process change control system in place to evaluate changes in starting materials, facilities, support systems, equipment, processing steps, and packaging materials that may affect the quality of APIs. (All systems)
- 13) Failure to maintain batch and quality control records. (Quality System)
- 14) Incomplete stability studies to establish API stability for the intended period of use, and/or failure to conduct forced degradation studies on APIs to isolate, identify and quantify potential degradants that may arise during storage. (Laboratory Control System)
- 15) Use of laboratory test methods that are inadequate or have not been validated; or the use of an inadequately qualified or untraceable reference standard. (Laboratory Control System)
- 16) Packaging and labeling in such a way that introduces a significant risk of mislabeling. (Packaging and Labeling System)

C. Veterinary Medical Devices

CVM establishment inspection coverage of veterinary medical devices and diagnostic aids should evaluate compliance with the Act. Examples of devices include such things as needles, syringes, surgical instruments, prosthetic devices, X-ray equipment, certain diagnostic test kits, dental appliances, examination gloves, sterile catheters, infusion pumps, etc. There is no CGMP or Quality System requirement applicable to the production of veterinary medical devices; however, veterinary medical devices may not be manufactured or held under insanitary conditions. Veterinary medical devices and diagnostic aid products may require the prescription legend and those intended for over the counter (OTC) use must bear adequate directions for use. Submission of a 510(k) or formal pre-market approval is *not* required for devices used in veterinary medicine.

For suspected violative veterinary medical devices, diagnostic aids, and residue screening tests, submit labeling to CVM/OSC/Division of Compliance (HFV-230) for review and comment. See additional information on how the Agency regulates these products at the following URL: [Animal Medical Devices | FDA](#)

D. 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. For inspections classified as OAI, the ORA Division should submit any recommendation for regulatory follow-up via CMS. If CVM feels an inspection classified as NAI or VAI should be classified as OAI, a request will be made to the Division to provide the full narrative EIR and exhibits through CMS for review. If CVM recommends an OAI reclassification, a meeting will be scheduled between the Division and CVM/DC. All compliance actions require CVM review and concurrence (i.e., direct reference is not provided).

The following are descriptions and examples of situations that may warrant inspectional classifications

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 within 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 actions pursuant to a surveillance inspection should result in the classification of all profile classes as unacceptable.
- Significant and wide-spread adverse conditions that are observed to directly affect animal drug products; or are very likely to lead to the adulteration of animal drug products.
- Systemic breakdown in any system of this compliance program that is likely to result in a human or animal health hazard(s).
- Analytical results from FDA official samples indicating animal drug 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.

E. 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 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 Good Manufacturing Practices (GMPs), 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). Additionally, if a foreign establishment or foreign government refuses a foreign inspection, the firm and its products may be subject to DWPE. 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"
- #68-09: "DETENTION WITHOUT PHYSICAL EXAMINATION OF NEW BULK ANIMAL DRUG SUBSTANCES"
- #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](#)

F. Exports

Section 801(e)(1) of the Act provides that unapproved new animal drugs may be exported if they meet certain conditions. Export certificates are issued by CVM/OSC/Division of Compliance (HFV-230). For additional information see Guidance for Industry - FDA Export Certificates at the following URL:

<http://www.fda.gov/RegulatoryInformation/Guidances/ucm125789.htm>.

PART VI - REFERENCES AND PROGRAM CONTACTS**6.1 – 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, Parts 11, 210, 211, 514, 520, 522, 524, 526, 528, 529 [Electronic Code of Federal Regulations \(eCFR\)](#)
3. Animal Drugs @ 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 [FDA Form 483 Frequently Asked Questions | FDA](#)
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:
 - Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients
 - Q9 Quality Risk Management
 - Q10 Pharmaceutical Quality System
13. The United States Pharmacopoeia / National Formulary (USP/NF) – [U.S. Pharmacopeia \(usp.org\)](#); <https://fda.sharepoint.com/sites/OIMT-FDAL-Library/SitePages/USP-NF.aspx>
14. [FMD 86: Establishment Inspection Report Conclusions and Decisions \(fda.gov\)](#)

FOOD AND DRUG ADMINISTRATION

COMPLIANCE PROGRAM

PROGRAM

7371.001

15. Compliance Program: 7356.002 – Drug Manufacturing Inspections ([CDER Compliance Programs – fda.gov](#))
16. Compliance Program: 7356.002A – Sterile Drug Process Inspections ([CDER Compliance Programs – fda.gov](#))
17. Compliance Program: 7356.002F – Active Pharmaceutical Ingredients ([CDER Compliance Programs – fda.gov](#))
18. 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](#))

6.2 – CONTACTS**A. Center Contacts**

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

Animal Drug Program Team, (HFV-233)
CVM/OSC/Division of Compliance
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 Surveillance
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 Reaction, Lack of Effectiveness, Product Defect Report contact:

CVM/OSC/Division of Veterinary Product Safety (HFV-240)
E-mail Address: CVMAESupport@fda.hhs.gov

B. 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