

SUBJECT: DRUG MANUFACTURING INSPECTIONS		IMPLEMENTATION DATE 2/1/2002
		COMPLETION DATE Continuing
DATA REPORTING		
PRODUCT CODES	PRODUCT/ASSIGNMENT CODES	
All Human Drugs Industry codes: 50, 54-56, 59, 60-66	Domestic / Foreign Inspections: 56002 56002A Sterile products manufacture 56002B Repackers and relabelers 56002C Radioactive drugs 56002E Compressed medical gases 56002F Bulk pharmaceutical chemicals	

FIELD REPORTING REQUIREMENTS

Forward a copy of each Establishment Inspection Report (EIR) for inspections classified as OAI due to CGMP deficiencies as part of any regulatory action recommendation submitted to HFD-300. For all inspections that result in the issuance of a Warning Letter, forward an electronic copy of each letter to the Division of Manufacturing and Product Quality, Case Management and Guidance Branch (HFD-325). An e-mail account has been established to receive copies of Warning Letters. The account e-mail address is CDERCGMPWL.

This program provides guidance in evaluating compliance with CGMP requirements. As soon as the District becomes aware of any significant inspectional, analytical, or other information developed under this program that may affect the agency's new drug approval decisions with respect to a firm, the District should report the information immediately according to current FACTS procedures. This includes filing OAI notifications and removing the notifications.

However, if information is encountered pertaining to inadequate postapproval reporting (Annual Reports, Supplements, Field Alert Reports, Adverse Drug Experience Reports, etc.) the information should be described in accordance with directions provided in those applicable compliance programs and under separate captions in the EIR. Data system information about these inspectional activities should be reported using applicable separate PAC(s). Expansion of coverage under these programs into a CGMP inspection must be reported under this compliance program.

The Districts are requested to use this revised compliance program for all GMP inspections.

PART I – BACKGROUND

A primary mission of the Food and Drug Administration is to conduct comprehensive regulatory coverage of all aspects of production and distribution of drugs and drug products to assure that such products meet the 501(a)(2)(B) requirements of the Act. FDA has developed two basic strategies:

- 1) evaluating through factory inspections, including the collection and analysis of associated samples, the conditions and practices under which drugs and drug products are manufactured, packed, tested and held, and
- 2) monitoring the quality of drugs and drug products through surveillance activities such as sampling and analyzing products in distribution.

This compliance program is designed to provide guidance for implementing the first strategy. Products from production and distribution facilities covered under this program are consistently of acceptable quality if the firm is operating in a state of control. The Drug Product Surveillance Program (CP 7356.008) provides guidance for the latter strategy.

The inspectional guidance 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 all processes is not feasible for all firms on a biennial basis. It also provides for follow-up compliance coverage as needed.

PART II - IMPLEMENTATION

OBJECTIVES

The goal of this program's activities is to minimize consumers' exposure to adulterated drug products.

Under this program, inspections and investigations, sample collections and analyses, and regulatory or administrative follow-up are made:

- 1) to determine whether inspected firms are operating in compliance with applicable CGMP requirements, and if not, to provide the evidence for actions to prevent adulterated products from entering the market and as appropriate to remove adulterated products from the market, and to take action against persons responsible as appropriate;
- 2) to provide CGMP assessment which may be used in efficient determination of acceptability of the firm in the pre-approval review of a facility for new drug applications;
- 3) to provide input to firms during inspections to improve their compliance with regulations; and,
- 4) to continue FDA's unique expertise in drug manufacturing in determining the adequacy of CGMP requirements, Agency CGMP regulatory policy, and guidance documents.

STRATEGY

A. Biennial Inspection of Manufacturing Sites (includes repackaging, contract labs, etc.)

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

Biennial inspections (every two years) conducted under this program:

- 1) reduce the risk that adulterated products are reaching the marketplace;
- 2) increase communication between the industry and the Agency;
- 3) provide for timely evaluation of new manufacturing operations in the firm; and,
- 4) provide for regular feedback from the Agency to individual firms on the continuing status of the firm's GMP compliance.

This program applies to all drug manufacturing operations.

Currently there are not enough FDA resources to audit every aspect of CGMP in every manufacturing facility during every inspection visit. Profile classes generalize inspection coverage from a small number of specific products to all the products in that class. This program establishes a systems approach to further generalize inspection coverage from a small number of profile classes to an overall evaluation of the firm. Reporting coverage for every profile class as defined in FACTS, in each biennial inspection, provides the most broadly resource-efficient approach. Biennial updating of all profile classes will allow for CGMP acceptability determinations to be made without delays resulting from revisiting the firm. This will speed the review process, in response to compressed time frames for application decisions and in response to provisions of the Food and Drug Administration Modernization Act of 1997 (FDAMA). This will allow for Pre-approval Inspections/Investigations Program inspections and Post-approval Audit Inspections Program inspections to focus on the specific issues related to a given application or the firm's ability to keep applications current.

The inspection is defined as audit coverage of 2 or more systems, with mandatory coverage of the Quality System (see system definitions below). Inspection options include different numbers of systems to be covered depending on the purpose of the inspection. Inspecting the minimum number of systems, or more systems as deemed necessary by the District, will provide the basis for an overall CGMP decision.

B. Inspection of Systems

Inspections of drug manufacturers should be made and reported using the system definitions and organization in this compliance program. Focusing on systems, rather than profile classes, will increase efficiency in conducting inspections because the systems are often applicable to multiple profile classes. One biennial inspection visit will result in a determination of acceptability/non-acceptability for all profile classes. Inspection coverage should be representative of all the profile classes manufactured by the firm. The efficiency will be realized because multiple visits to a firm will not be needed to cover all profile classes; delays in approval decisions will be avoided because up-to-date profile class information will be available at all times.

Coverage of a system should be sufficiently detailed, with specific examples selected, so that the system inspection outcome reflects the state of control in that system for every profile class. If a particular system is adequate, it should be adequate for all profile classes manufactured by the firm. For example, the way a firm handles "materials" (i.e., receipt, sampling, testing, acceptance, etc.) should be the same for all 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. Under each system there may be something unique for a particular profile class: e.g., under the Materials System, the production of Water for Injection USP for use in manufacturing. 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.

Complete inspection of one system may necessitate further follow up of some items within the activities of another/other system(s) to fully document the findings. However, this coverage does not constitute nor require complete coverage of these other systems.

C. 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 cGMPs and internal procedures and specifications. The system includes the quality control unit and all of its review and approval duties (e.g., change control, reprocessing, batch release, annual record review, validation protocols, and reports, etc.). It includes all product defect evaluations and evaluation of 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 HVAC, compressed gases, steam and water systems.

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

2. 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, 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 methods development and validation or verification, and the stability program. See the CGMP regulation, 21 CFR 211 Subparts B, I, J, and K.

The overall theme in devising this scheme of systems was the subchapter structure of the CGMP regulation. Every effort was made to group whole subchapters together in a rational set of six systems which incorporates the general scheme of pharmaceutical manufacturing operations.

The organization and personnel, including appropriate qualifications and training, employed in any given system, will be evaluated as part of that system's operation. 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. Inspections of contract companies should be within the system for which the product or service is contracted as well as their Quality System.

As this program approach is implemented, the experience gained will be reviewed to make modifications to the system definitions and organization as needed.

PROGRAM MANAGEMENT INSTRUCTIONSA. Definitions1. Surveillance InspectionsThe 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 firm's CGMP. This will be done when little or no information is known about a firm's CGMP compliance (e.g., for new firms); or for firms where there is doubt about the CGMP compliance in the firm (e.g., a firm whose history has documented short-lived compliance and recidivism); or follow up to previous regulatory actions. Based on findings of objectionable conditions as listed in Part V in one or more systems (a minimum of two systems must be completed), a Full Inspection may revert to the Abbreviated Inspection Option, with District concurrence. See Part III, Section B.1. During the course of a Full Inspection, verification of Quality System activities may require limited coverage in other systems. 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 system which includes the responsibility for the annual product reviews).

The Abbreviated Inspection Option

The Abbreviated Inspection Option is a surveillance or compliance inspection which is meant to provide an efficient update evaluation of a firm's CGMP. The abbreviated inspection will provide documentation for continuing a firm in a satisfactory CGMP compliance status. Generally this will be done when a firm has a record of satisfactory CGMP compliance, with no significant recall, or product defect or alert incidents, or with little shift in the manufacturing profiles of the firm within the previous two years. See Part III, Section B.2. A Full Inspection may revert to an Abbreviated Inspection based on findings of objectionable conditions as listed in Part V in one or more systems. The Abbreviated Inspection Option normally will include an inspection audit of at least two of the systems, one of which must be the Quality System (the system which includes the responsibility for the annual product reviews). The District drug program managers should ensure that the optional systems are rotated in successive Abbreviated Inspections. During the course of an abbreviated inspection, verification of quality system activities may require limited coverage in other systems. Some firms participate in a limited part of the production of a drug or drug product, e.g., a contract laboratory. Such firms may employ only two of the systems defined. In these cases the inspection of the two systems will comprise inspection of the entire firm and will be considered the Full Inspection Option.

Selecting Systems for Coverage

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

2. Compliance Inspections

Compliance Inspections are inspections done to evaluate or verify compliance corrective actions after a regulatory action has been taken. First, the coverage given in compliance inspections must be related to the areas found deficient and subjected to corrective actions.

In addition, coverage must be given to systems because a determination must be made on the overall compliance status of the firm after the corrective actions are taken. The firm is expected to address all of its operations in its corrective action plan after a previously violative inspection, not just the deficiencies noted in the FDA-483. The Full Inspection Option should be used for a compliance inspection, especially if the Abbreviated Inspection Option was used during the violative inspection.

Compliance Inspections include For Cause Inspections. For Cause Inspections are compliance inspections which are done to investigate a specific problem that has come to the attention of some level of the agency. The problems may be indicated in Field Alert Reports (FARs), industry complaints, recalls, indicators of defective products, etc. Coverage of these areas may be assigned under other compliance programs, however, expansion of the coverage to a GMP inspection is to be reported under this program. For Cause Inspections may be assigned under this program as the need arises.

3. State of Control

A drug firm is considered to be operating in a state of control when it employs conditions and practices that assure compliance with the intent of Sections 501(a)(2)(B) of the Act and portions of the CGMP regulations that pertain to their systems. A firm in a state of control produces finished drug products for which there is an adequate level of assurance of quality, strength, identity and purity.

A firm 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/those system(s) cannot be adequately assured. Documented CGMP deficiencies provide the evidence for 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 systems/firm.

4. 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.

5. Drug Manufacturing Inspection

A drug manufacturing inspection is a factory inspection in which evaluation of two or more systems, including the Quality System, is done to determine if manufacturing is occurring in a state of control.

B. Inspection Planning

The Field will conduct drug manufacturing inspections and maintain profiles or other monitoring systems which will ensure that each drug firm receives biennial inspectional coverage, as provided for in the strategy.

The District Office is responsible for determining the depth of coverage given to each drug firm. CGMP inspectional coverage shall be sufficient to assess the state of compliance for each firm.

The frequency and depth of inspection should be determined by the statutory obligation, the firm's compliance history, the technology employed, and the characteristics of the products. When a system is inspected, the inspection of that system may be considered applicable to all products which use it. Investigators should select an adequate number and type of products to accomplish coverage of the system. Selection of products should be made so that coverage is representative of the firm's overall abilities in manufacturing within CGMP requirements.

Review of NDA/ANDA files may assist in selecting significant drug processes for coverage in the various systems. Significant drug processes are those which utilize all the systems in the firm very 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 drug application, should be considered first in selecting products for coverage.

The health significance of certain CGMP deviations may be lower when the drug product involved has no major systemic effect or no dosage limitations such as in products like calamine lotion or OTC medicated shampoos. Such products should be given inspection coverage with appropriate priority.

Inspections for this compliance program may be performed during visits to a firm when operations are being performed for other compliance programs or other investigations.

C. Profiles

The inspection findings will be used as the basis for updating all profile classes in the profile screen of the FACTS EIR coversheet that is used to record profile/class determinations. Normally, an inspection under this systems approach will result in all profile classes being updated.

PART III - INSPECTIONALINVESTIGATIONAL OPERATIONSA. General

Review and use the CGMPs for Finished Pharmaceuticals (21 CFR 210 and 211) to evaluate manufacturing processes. Use Guides to Inspection published by the Office of Regional Operations for information on technical applications in various manufacturing systems.

The investigator should conduct inspections according to the STRATEGY section in Part II of this compliance program. Recognizing that drug firms vary greatly in size and scope, and manufacturing systems are more or less sophisticated, the approach to inspecting each firm should be carefully planned. For example, it may be more appropriate to review the Quality System thoroughly before entering production areas in some firms; in others, the Quality System review should 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 firm, but also one which directs the performance and reporting on the inspection within a framework which will provide for a uniform level of CGMP assessment. Furthermore, this inspection approach will provide for fast communication and evaluation of findings.

Inspectional Observations noting CGMP deficiencies should be related to a requirement. Requirements for manufacture of drug products (dosage forms) are in the CGMP regulation and are amplified by policy in the Compliance Policy Guides, case precedents, etc. CGMP requirements apply to the manufacture of distributed prescription drug products, OTC drug products, approved products and products not requiring approval, as well as drug products used in clinical trials. The CGMP regulations are not direct requirements for manufacture of API's; the regulations should not be referenced as the basis for a GMP deficiency in the manufacture of Active Pharmaceutical Ingredients (APIs), but they are guidance for CGMP in API manufacture.

Guidance documents do not establish requirements. They state examples of ways to meet requirements. Guidance documents are not to be referred to as the justification for an inspectional observation. The justification comes from the CGMPs. Current Guides to Inspection and Guidance to Industry documents provide interpretations of requirements, which may assist in the evaluation of the adequacy of CGMP systems.

Current inspectional observation policy as stated in the IOM says that the FDA-483, when issued, should be specific and contain only significant items. For this program, inspection observations should be organized under separate captions by the systems defined in this program. List observations in order of importance within each system. Where repeated or similar observations are made, they should be consolidated under a unified observation. For those Districts utilizing Turbo EIR, a limited number of observations can be common to more than one system (e.g. organization and personnel including appropriate qualifications and training). In these instances, put the observation in the first system reported

on the FDA-483 and in the text of the EIR, reference the applicability to other systems where appropriate. This is being done to accommodate the structure of Turbo EIR which allows individual citation once per FDA-483. Refrain from using unsubstantiated conclusions. Do not use the term "inadequate" without explaining why and how. Refer to policy in the IOM, Chapter 5, Section 512 and Field Management Directive 120 for further guidance on the content of Inspectional Observations.

Specific specialized inspectional guidance may be provided as attachments to this program, or in requests for inspection, assignments, etc.

B. Inspection Approaches

This program provides two surveillance inspectional options, Abbreviated Inspection Option and Full Inspection Option. See the definitions of the inspection options 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 in Part II Strategy, one of which must be the Quality System.
 - a. Select the Full Inspection Option for an initial FDA inspection of a facility. A Full Inspection may revert to the Abbreviated Inspection Option, **with District concurrence**, based on finding of objectionable conditions as listed in Part V in one or more systems (a minimum of two systems must be completed).
 - b. Select the Full Inspection Option when the firm has a history of fluctuating into and out of compliance. To determine if the firm meets this criterion, the District should utilize all information at its disposal, such as, inspection results, results of sample analyses, complaints, DQRS reports, recalls, etc. and the compliance actions resulting from them or from past inspections. A Full Inspection may revert to the Abbreviated Inspection Option, **with District concurrence**, based on findings of objectionable conditions as listed in Part V in one or more systems (a minimum of two systems must be completed).
 - c. Evaluate if important changes have occurred by comparing current operations against the EIR for the previous Full Inspection. The following types of changes are typical of those that warrant the Full Inspection Option:
 - (1) New potential for cross-contamination arising through change in process or product line.
 - (2) Use of new technology requiring new expertise, significant new equipment, or new facilities.
 - d. A Full Inspection may also be conducted on a surveillance basis at the District's discretion.
 - e. The Full Inspection Option will satisfy the biennial inspection requirement.

- f. Follow up to a Warning Letter or other significant regulatory actions should require a Full Inspection option.
2. Selecting the Abbreviated Inspection Option. The Abbreviated Inspection Option normally will include inspection audit of at least two 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.
- a. This option involves an inspection of the manufacturer to maintain surveillance over the firm's activities and to provide input to the firm on maintaining and improving the GMP level of assurance of quality of its products.
 - b. A Full Inspection may revert to the Abbreviated Inspection option, **with District concurrence**, based on findings of objectionable conditions as listed in Part V in one or more systems (a minimum of two systems must be completed).
 - c. An abbreviated inspection is adequate for routine coverage and will satisfy the biennial inspectional requirement.

Comprehensive Inspection Coverage

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

C. System Inspection Coverage

QUALITY SYSTEM

Assessment of the Quality System is two phased. The first phase is to evaluate whether the Quality Control Unit has fulfilled the 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 and may link to other major systems for inspectional coverage.

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm's adherence to written procedures should be verified through observation whenever possible. These areas are not limited to finished products, but may also incorporate components and in-process materials. These areas may indicate deficiencies not only in this system but also in other major systems that would warrant expansion of coverage. All areas under this system should be covered; however the depth of coverage may vary depending upon inspectional findings.

- Product reviews: at least annually; should include information from areas listed below as

- appropriate; batches reviewed, for each product, are representative of all batches manufactured; trends are identified; refer to 21 CFR 211.180(e).
- Complaint reviews (quality and medical): documented; evaluated; investigated in a timely manner; includes corrective action where appropriate.
 - 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
 - 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.

FACILITIES AND EQUIPMENT SYSTEM

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm's adherence to written procedures should be verified through observation whenever possible. 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 listed below should be covered; however, the depth of coverage may vary depending upon inspectional findings.

1. 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 firm to prevent contamination or mix-ups
- general air handling systems
- control system for implementing changes in the building
- lighting, potable water, washing and toilet facilities, sewage and refuse disposal
- sanitation of the building, use of rodenticides, fungicides, insecticides, cleaning and sanitizing agents

2. Equipment

- equipment installation and operational qualification where appropriate
- adequacy of equipment design, size, and location
- equipment surfaces should not be 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
- 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 (where appropriate)
- documented investigation into any unexpected discrepancy

MATERIALS SYSTEM

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm's adherence to written procedures should be verified through observation whenever possible. These areas are not limited to finished products, but may also incorporate components 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 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 firm'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
- 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 processes
- finished product distribution records by lot
- documented investigation into any unexpected discrepancy

PRODUCTION SYSTEM

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm's adherence to written procedures should be verified through observation whenever possible. These areas are not limited to finished products, but may also incorporate components 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 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
- formulation/manufacturing at not less than 100%
- 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 objectionable microorganisms in non-sterile drug products
- adherence to preprocessing procedures (e.g., set-up, line clearance, etc.)
- equipment cleaning and use logs
- master production and control records
- batch production and control records
- process validation, including validation and security of computerized or automated processes
- change control; the need for revalidation evaluated
- documented investigation into any unexpected discrepancy

PACKAGING AND LABELING SYSTEM

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm'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 components 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 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 they 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
- conformance to tamper-evident (TEP) packaging requirements (see 21CFR 211.132 and Compliance Policy Guide, 7132a.17)
- validation of packaging and labeling operations including validation and security of computerized processes
- documented investigation into any unexpected discrepancy

LABORATORY CONTROL SYSTEM

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm'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 components 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 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 processes
- 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. 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. Districts 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 range of toxicity, or a low dosage strength. Include samples of products of minimal therapeutic significance only when they illustrate highly significant CGMP deficiencies.

For sampling guidance, refer to IOM, Chapter 4

E. Inspection Teams

An inspection team (See IOM 502.4) composed of experts from within the District, other Districts, or Headquarters is encouraged when it provides needed expertise and experience. Contact ORO/Division of Field Investigations 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 ORO/Division of Field Science.

F. Reporting

The investigator will utilize Subchapter 590 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

ANALYZING LABORATORIES

1. Routine chemical analyses - all Servicing Laboratories except WEAC.

2. Sterility testing:

<u>Region</u>	<u>Examining Laboratory</u>
NE	NRL
SE	SRL
CE	NRL
SW, PA	SAN-DO

3. Other microbiological examinations - NRL (for the CE Region), SRL, SAN, and DEN.

Salmonella Serotyping Lab - ARL

4. Chemical cross-contamination analyses by mass spectrometry (MS) – NRL, SRL, DEN, PRL/NW, and PHI. Non-mass spectrometry laboratories should call one of their own regional MS capable laboratories or Division of Field Science (HFC-140) to determine the most appropriate lab for the determinations to be performed.

5. Chemical cross-contamination analyses by Nuclear Magnetic Resonance (NMR) spectroscopy - NRL. Non-NMR laboratories should call one of their own regional labs equipped with NMR or Division of Field Science (HFC-140) to determine the most appropriate lab for the determinations to be performed.

6. Dissolution testing – NRL, KAN, SRL, SJN, DET, PHI, DEN, PRL/SW and PRL-NW. Districts without dissolution testing capability should use one of their own regional labs for dissolution testing. Otherwise, call DFS.

7. Antibiotic Analyses:

ORA Examining Laboratory

Denver District Lab (HFR-SW260)

Tetracyclines
Erythromycins

Northeast Regional Lab (HFR-NE500)

Penicillins
Cephalosporins

CDER Examining Laboratory

Office of Testing and Research
Division of Pharmaceutical Analysis
(HFD-473)
All other Antibiotics

7. Bioassays - Division of Testing and Applied Analytical Research, Drug Bioanalysis Branch (HFN-471).
9. Particulate Matter in Injectables: NRL, SRL.
10. Pyrogen/LAL Testing: SRL

ANALYSIS:

1. Samples are to be examined for compliance with applicable specifications as they relate to deficiencies noted during the inspection. Check analyses will be by the official method, or when no official method exists, by other validated procedures. See CPG 7152.01.
2. The presence of cross-contamination must be confirmed by a second method. Spectroscopic methods, such as MS, NMR, UV-Visible, or infrared (IR) are preferred. A second confirmatory method should be employed by different mechanisms than the initial analysis (i.e., ion-pairing vs. conventional reverse phase HPLC).
3. Check Analysis for dissolution rate must be performed by a second dissolution-testing laboratory.
4. Sterility testing methods should be based on current editions of USP and the Sterility Analytical Manual. Other microbiological examinations should be based on appropriate sections of USP and BAM.

PART V - REGULATORY/ADMINISTRATIVE STRATEGY

Inspection findings that demonstrate that a firm is not operating in a state of control may be used as evidence for taking appropriate advisory, administrative and/or judicial actions.

When the management of the firm is unwilling or unable to provide adequate corrective actions in an appropriate time frame, formal agency regulatory actions will be recommended, designed to meet the situation encountered.

When deciding the type of action to recommend, the initial decision should be based on the seriousness of the problem and the most effective way to protect consumers. Outstanding instructions in the Regulatory Procedures Manual (RPM) should be followed.

The endorsement to the inspection report should point out the actions that have been taken or will be taken and when. All deficiencies noted in inspections/audits under this program must be addressed by stating the firm's corrective actions, accomplished or projected, for each as established in the discussion with management at the close of the inspection.

All corrective action approaches in domestic firms are monitored and managed by the District Offices. 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. CDER/DMPQ/CMGB/HFD-325 will assist District Offices as requested.

An inspection report that documents that one or more systems is/are out of control should be classified OAI. District Offices may issue Warning Letters per RPM, Chapter 4, to warn firms of violations, to solicit voluntary corrections, and to provide for the initial phase of formal agency regulatory actions.

Issuance of a Warning Letter or taking other regulatory actions pursuant to a surveillance inspection (other than a For Cause Inspection) should result in the classification of all profile classes as unacceptable. Also, the inspection findings will be used as the basis for updating profile classes in FACTS.

FDA laboratory tests which demonstrate effects of absent or inadequate current good manufacturing practice are strong evidence for supporting regulatory actions. Such evidence development should be considered as an inspection progresses and deficiencies are found. However, the lack of violative physical samples is not a barrier to pursuing regulatory and/or administrative action provided that CGMP deficiencies have been well documented. Likewise, physical samples found to be in compliance are not a barrier to pursuing action under CGMP charges.

Evidence to support significant and/or a trend of deficiencies within a system covered could demonstrate the failure of a system and should result in consideration of the issuance of a Warning Letter or other regulatory action by the District. 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 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 GMP 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 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 intended use of the water.
- 6) Lack of validation of computerized processes.

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 processes.
- 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 processes.
- 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 and/or automated processes.
- 4) Pattern of inadequate sampling practices.
- 5) Lack of validated analytical methods.
- 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 stability programs.

Follow up to a Warning Letter or other significant regulatory action as a result of an Abbreviated Inspection should warrant Full Inspection coverage as defined in this program.

PART VI - REFERENCES, ATTACHMENTS, AND PROGRAM CONTACTS**REFERENCES**

1. Federal Food, Drug, and Cosmetic Act, as amended
2. Code of Federal Regulations, Title 21, Parts 210 and 211, as revised, including the General Comments (preamble)
3. Compliance Policy Guides Manual, Chapter 4 Human Drugs
4. Compressed Medical Gases Guideline
5. Guideline on General Principles of Process Validation
6. Guideline on Sterile Drug Products Produced by Aseptic Processing
7. Guide to Inspection of Computerized Systems in Drug Processes
8. Regulatory Procedures Manual, Part 8
9. Inspection Operations Manual (IOM)
10. Guide to Inspections of Dosage Form Drug Manufacturers-CGMPs
11. Guide to Inspections of Lyophilization of Parenterals
12. Guide to Inspections of Pharmaceutical Quality Control Laboratories
13. Guide to Inspections of High Purity Water Systems
14. Guide to Inspections of Validation of Cleaning Processes
15. Guidance to Industry (Draft) Investigation of OOS Test Results
16. 21 CFR Part 11 Electronic Records: Electronic Signatures
17. Compliance Policy Guide 7153.17 Enforcement Policy, Part 11 Electronic Records; Electronic Signatures
18. Electronic Records Guide (4/21/98) (Electronic Signatures, 21 CFR Part 11 Answers to Frequently Asked Questions)

Attachments

Attachments to the Drug Process Inspection program may be issued for certain industries, dosage forms, and processes with known problems or unique drug processes. These attachments will contain the guidance needed to perform these specialized inspections.

Some of the attachments to be issued with this program may include reporting requirements specifically designed to obtain industry-wide information on certain practices to permit evaluation of the adequacy of FDA's regulatory efforts.

Attachments and/or reporting requirements will be periodically reviewed and evaluated and deleted from the program when they are no longer needed.

CONTACTS

ORA

ORO/Division of Field Investigations/Drug Group (HFC-132)
Telephone: (301) 827-5653

ORO/Division of Field Science (HFC-140)
Telephone: (301) 827-7605

Center for Drug Evaluation and Research

CGMP Questions

Division of Manufacturing & Product Quality
Chief, Case Management and Guidance Branch (HFD-325)
Telephone: (301) 594-0098
Fax: (301) 594-2202

Product Quality Problems (NDA/ANDA/Compendial Specifications deviations)

Division of Manufacturing & Product Quality
Chief, Case Management & Guidance Branch (HFD-325)
Telephone: (301) 594-0098
Fax: (301) 594-2202

Product Quality Problems (Drug Product Sampling, FAR reporting, ADE reporting)

Team Leader, Post Market Surveillance Team (HFD-336)
Division of Rx Drug Compliance and Surveillance
Telephone: (301) 594-0101
Fax: (301) 594-1146

PART VII - CENTER RESPONSIBILITIES

CENTER FOR DRUG EVALUATION AND RESEARCH

The Division of Manufacturing and Product Quality (DMPQ) HFD-320 will conduct an annual evaluation in order to assess and report on the effectiveness of this program.

Please send any comments on the operation and efficiency and direct any questions regarding application of the program to the Chief, Case Management and Guidance Branch, DMPQ, HFD-325, 301-594-0098, fax 301-594-2202.