

CHAPTER 56 – DRUG QUALITY ASSURANCE

SUBJECT: ACTIVE PHARMACEUTICAL INGREDIENT (API) PROCESS INSPECTION Revision Summary: Program remains current; minor changes made 4/2013 to update offices and contacts, data codes, and references.		IMPLEMENTATION DATE February 13, 2006
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DATA REPORTING		
PRODUCT CODES	PRODUCT/ASSIGNMENT CODES	
Industry codes 54, 56 and 60-66 inclusive	Domestic / Foreign Inspections: 56002F (Full Inspection) 56002L (Abbreviated Inspection) Related PACs 56002 & H – Drug Process Inspections (DPI) 56002C & K – DPI / Radioactive Drugs 56002M – DPI/Therapeutic Biological Product Inspections	

FIELD REPORTING REQUIREMENTS

Forward a copy of each Establishment Inspection Report (EIR) for inspections classified as Official Action Indicated (OAI) due to current good manufacturing practice (CGMP) deficiencies as part of any regulatory action recommendation submitted to CDER Office of Compliance, Office of Manufacturing and Product Quality. For all **domestic** inspections that result in a recommendation to CDER for regulatory action based on current good manufacturing practice deficiencies, forward the recommendation and any associated documentation to CDER and other offices as specified in the Regulatory Procedures Manual. Warning Letter recommendations, with a copy of the proposed Warning Letter and supporting documents, should be sent to CDER’s Office of Manufacturing and Product Quality (OMPQ), Division of Domestic Drug Quality using CMS. All other regulatory action recommendations and associated documentation based on domestic inspection are to be directed to CDER’s Office of Compliance using CMS. For all **foreign** inspections, regardless of inspection outcome, forward the complete and original EIR, including exhibits, to OMPQ/ Division of International Drug Quality. See Part III, *Special Instructions for Foreign Drug Inspections*.

This program provides guidance in evaluating compliance with CGMP and providing comprehensive regulatory coverage of all aspects of production and distribution of active pharmaceutical ingredients (APIs) to assure that such products comply with Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act). 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 and abbreviated new drug approval decisions

with respect to a firm, the District should report the information immediately according to current FACTS and EES procedures. This includes promptly filing and deleting OAI notifications.

Districts are to use this revised compliance program for CGMP inspections of API facilities.

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PART I - BACKGROUND

GENERAL

APIs are subject to the adulteration provisions of Section 501(a)(2)(B) of the Act, which requires all drugs to be manufactured in conformance with CGMP. No distinction is made between an API and a finished pharmaceutical in the Act and the failure of either to comply with CGMP constitutes a violation of the Act. FDA has not promulgated CGMP regulations specifically for APIs or drug components (as we have for finished pharmaceuticals). Thus, the use of “CGMP” in this document refers to the requirements of the Act rather than the requirements of 21 CFR Parts 210 and 211 regulations for finished pharmaceuticals.

FDA has long recognized that the CGMP requirements in the good manufacturing practice regulations for finished pharmaceuticals (21 CFR Parts 210 and 211) are valid and applicable in concept to active pharmaceutical ingredient (API) manufacturing. These concepts include, among others, building quality into the drug by using suitable equipment and employing appropriately qualified and trained personnel, establishing adequate written procedures and controls designed to assure manufacturing processes and controls are valid, establishing a system of in-process material and final drug tests, and ensuring stability of drugs for their intended period of use. In 2001, FDA adopted an internationally harmonized guidance to industry on API CGMPs in conjunction with regulatory partners in the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). This guidance is ICH Q7, *Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*. ICH Q7 represents the Food and Drug Administration’s (FDA’s) current thinking on CGMPs for API’s. Thus, API and related manufacturing and testing facilities that follow this guidance generally will be considered to comply with the statutory CGMP requirement. However, alternate approaches may be used if such approaches satisfy the requirements of Section 501(a)(2)(B) of the Act as long as the approach ensure that the API meets its purported or represented purity, identity, and quality characteristics.

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 defined in ICH Q7 as “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 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. “Drug substance” and “bulk pharmaceutical chemical” (BPC) are terms commonly used to mean API and, for BPC, inactive ingredients. The use of these terms to describe active ingredients may be considered equivalent to the term used here, API.

FDA expects API manufacturers to apply CGMPs to the API process beginning with the use of starting materials, and to validate critical process steps that impact the quality and purity of the final API. Controls over material quality are expected to increase as the process approaches the final API. The level of control needed is highly dependent on the manufacturing process and increases throughout the process as it proceeds from early intermediate steps to final isolation

and purification steps. The appropriate level of control depends on the risk or criticality associated with each specific process step.

ICH Q7 contains general guidance to industry on the extent and application of CGMP for manufacturing APIs under an appropriate system for managing quality. It is also intended to help ensure that APIs meet the quality and purity characteristics that they purport or are represented to possess. ICH Q7 is to be used as a guideline for inspecting API manufacturers and related facilities. If an investigator believes that a particular practice conforming to this guidance is believed to be deficient, the investigator or district should consult with CDER DMPQ before making an observation that is in conflict with ICH Q7. A firm may also use alternate approaches to those described in ICH Q7.

API manufacturers must register and APIs in commercial distribution must be listed under section 510(g) of the Act unless exempted under 21 CFR 207.10. Foreign drug manufacturers are also required to register and list all drugs imported or offered for import into the United States. Refer to 21 CFR 207.40 for additional information on establishment registration and drug listing requirements for foreign drug facilities.

The inspection guidance in this program is structured for the efficient use of resources planned for routine surveillance coverage of API manufacturing facilities, 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.

SCOPE OF APIs COVERED BY THIS PROGRAM

An API process is a related series of operations which result in the preparation of an active pharmaceutical ingredient. Major operations or steps in an API process may include multi-step chemical synthesis and fermentation, purification, crystallization, drying, milling, packing, labeling, and testing.

Some drugs processed similarly to an API may in fact be bulk finished product and subject to the requirements of 21 CFR Parts 210 and 211. If the drug material will not undergo further processing or compounding after its synthesis/fermentation/extraction, but is merely repackaged into market containers, it is a bulk finished product. However, investigators should use this program as guidance when covering the synthesis/fermentation processes that result in such APIs rather than the program for dosage forms (CP 7356.002).

This program does not cover all vaccines, whole cells, whole blood and plasma, blood and plasma derivatives (plasma fractionation), and gene therapy APIs as these drugs are regulated under the jurisdiction of the Center for Biologics Evaluation and Research.

The following APIs are to be inspected using CP7256.002M, Inspections of Licensed Biological Therapeutic Drug Products:

- biotechnology-derived APIs, including those expressed from mammalian or bacterial cell cultures
- polypeptides

Neither this compliance program nor ICH Q7 will provide guidance on the sterilization and aseptic processing of sterile APIs (see Q7 Section 1.3). Investigators are to use the finished product regulations (21 CFR 210 and 211) as guidance and follow CP 7356.002A, *Sterile Drug Process Inspections*, when inspecting the sterile processing of APIs labeled as sterile. Investigators are also to use FDA guidance on aseptic processing, *Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice*, 2004, in evaluating aseptic processing conditions for sterile APIs.

[end Part I]

PART II - IMPLEMENTATION

OBJECTIVE

The primary objective of this compliance program is to provide comprehensive CGMP inspectional coverage of the domestic and foreign API industry in all profile classes (i.e., types of API manufacturing processes) to determine whether a manufacturer is operating in a state of control. An API manufacturer is considered to be operating in a state of control when it employs conditions and practices that assure compliance with the intent of Section 501(a)(2)(B) of the Act. A firm in a state of control produces APIs for which there is an adequate level of assurance of quality, identity and purity.

A firm is not in a sufficient state of control if any one system, as defined in this program, is found to be significantly non-compliant with CGMPs, such that the quality, identity and purity of the API resulting from that system 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 that a system(s) is not in a state of control.

Profile classes generalize inspection coverage from a small number of specific APIs to all APIs 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. This allows for pre-approval program inspections to focus on the specific issues related to a given application and improves the review process by providing timely and efficient support for application decisions.

Inspection of API manufacturers should be conducted and reported using the system definitions and organization in this compliance program. Focusing on systems, rather than just profile classes, will increase efficiency in conducting inspections because the systems are often applicable to multiple profile classes. An inspection under this program is profileable and will result in a determination of acceptability/non-acceptability for all API profile classes. Inspection coverage should be representative of all API profile classes manufactured by the firm. All other profile classes should be covered under the main program CP 7356.002, or related program circular, as appropriate. Other objectives include:

- Obtain information on operations impacting on sterility, to identify areas for improvement and correction.
- Evaluate current good manufacturing practices in the sterile drug industry.
- Initiate appropriate action against manufacturers observed to be out of compliance.

PROGRAM MANAGEMENT INSTRUCTIONS

The Field will conduct API manufacturing inspections and maintain profiles or other monitoring systems with the goal that each API firm will receive biennial inspectional coverage. CDER will also identify firms for inspection coverage under this program to fulfill CDER and agency annual performance goals and as part of an initiative to ensure risk-based prioritization of inspection coverage.

Unless specifically directed by CDER, the District Office is responsible for determining the frequency and depth of coverage given to each API firm consistent with this compliance program's instructions. CGMP inspectional coverage under this program shall be sufficient to assess the state of compliance for each firm.

An inspection under this program is defined as audit coverage of 2 or more systems (the "systems" are defined below in this section and are consistent with the main program, 7356.002), with mandatory coverage of the Quality System. Inspecting at least two systems (i.e., the Quality System and one other system) will provide the basis for an overall CGMP decision.

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 representative system is adequate, it should be adequate for all profile classes manufactured by the firm.

If an API selected for inspection coverage is associated with a unique processing or control function in a system not chosen for coverage you may cover the unique function for that API. In doing so, you need not give full coverage to that system. For example, if an API chosen for coverage uses high purity water alone in its manufacture, you may inspect the water purification system without having to give full inspection coverage of the Materials System.

In some circumstances, it may not be possible to generalize certain deficiencies in a system to all API profile classes. If so, the unaffected profile classes may be considered acceptable if found otherwise acceptable.

Selecting unique functions within a system will be at the discretion of the investigator. Any given inspection need not cover every system.

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

A general scheme of systems for auditing the manufacture of API consists of the following:

1. **Quality System** assures overall compliance with CGMPs and internal procedures and specifications.
2. **Facilities and Equipment System** includes activities which provide an appropriate physical environment and resources used in the production of APIs.
3. **Materials System** includes measures and activities to control starting materials, intermediates, and containers. It includes validation of computerized and inventory control processes, storage, and distribution controls.
4. **Production System** includes measures and activities to control the manufacture of APIs, including in-process sampling and testing, and process validation.
5. **Packaging and Labeling System** includes measures and activities that control the packaging and labeling of intermediates and APIs.

6. **Laboratory Control System** includes measures and activities related to laboratory procedures, testing, analytical methods development and methods validation or verification, and the stability program.

Detailed inspection coverage guidance under these systems is given in Appendix A of this program.

INSPECTION PLANNING

This program is intended to provide for a risk-based inspection strategy. Inspection depth should therefore reflect appropriate risks associated with a particular firm’s operations, such as the firm’s compliance history, the technology employed, the labeled and purported characteristics, and the intended use in the finished product, if known, of the APIs.

When a system is inspected, the inspection of that system may be considered applicable to all API products which use it. Investigators should select an adequate number and type of APIs to accomplish coverage of the system. APIs selected for coverage should be representative of the firm’s overall abilities in manufacturing within CGMPs. (A profile classification scheme is used to categorize APIs by the nature of their processing, as described below.)

Profile class codes or APIs selected for coverage are to be representative of all APIs processed at the firm being inspected. Profile class codes may also be grouped by similarity, such that coverage of one profile class is sufficient to demonstrate CGMP conditions for another profile class. For example, inspecting a CSS API could amount to surrogate coverage of CSN. Similarly, inspecting a CBI could amount to surrogate coverage of other profile classes, such as CFN, CFS, and perhaps CEX.

The public health significance of certain CGMP deviations may be lower when the API is intended for a dosage form that has no dosage limitation, such as in products like calamine lotion or some OTC medicated shampoos. Such APIs should be given inspection coverage of reduced depth and intensity.

Profile Classes

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 system approach will result in all profile classes being updated. Effective with this program circular are a list of profile class codes that are used to report the processes covered during API inspections. These are:

PROFILE CLASS	FULL DESCRIPTION
CBI	Biotechnology derived API (sterile and non-sterile)
CEX	Plant/Animal Extraction API
CFN	Non Sterile API by Fermentation
CFS	Sterile API by Fermentation
CRU	Non-sterile/intermediate/NEC inorganic/mineral (not plant/animal)
	<i>(table continued on next page)</i>

PROFILE CLASS	FULL DESCRIPTION
CRX	Sterile starting/intermediate/NEC (not plant/animal)
CSN	Non Sterile API by Chemical Synthesis
CSS	Sterile API by Chemical Synthesis
CTL	Control Testing Laboratory
CTX	Testing Laboratory plus Manufacturer
CXA	Purified API derived from plant/animal extraction

TYPES OF INSPECTIONS

There are two basic types of inspections: surveillance and compliance. Surveillance inspections are conducted on a routine basis to satisfy FDA's responsibilities to inspect drug manufacturing facilities. Compliance inspections are conducted in response to violative surveillance inspections and when a need arises to inspect a facility for-cause.

This program follows the approach in the main compliance program, 7356.002. There are two alternate approaches to inspecting a facility to satisfy FDA inspection obligations; these are termed "Full Inspection" and "Abbreviated Inspection." These are described in Part III, *Inspectional*, of this program.

[end Part II]

PART III - INSPECTIONAL

Inspections of API manufacturers, whether foreign or domestic, should be conducted by experienced investigators with education and/or training particularly in fermentation (see also 7356.002M for additional inspection guidance) and chemical synthesis manufacturing methods. Use of chemists and/or microbiologists during API inspections is recommended, particularly for evaluating laboratory operations (e.g., analytical methods evaluation, analytical data, lab procedures and instrumentation), analytical review of methods used to establish impurity profiles, fermentation manufacturing processes, and complex multi-step chemical synthesis processes.

Investigators conducting API inspections must understand the basic differences between the processes used for the production of APIs and those used for finished dosage forms. APIs are usually produced by chemical synthesis or by cell culture and extraction. Thus, the production of APIs typically involves significant changes of starting materials or intermediates by various chemical, physical, and biological processing steps. The ultimate objective in API processing generally is to achieve a pure compound of certain identity, whereas the ultimate objective of finished dosage form manufacturing generally is to achieve the uniform distribution of an API among many dosing units designed to deliver a precise amount of API to a specific area of the body.

Since manufacturers of APIs are often referenced in many drug applications, each inspection should cover representative APIs when covering the systems selected (e.g., if inspecting the Production System for a site making an API by fermentation and another by synthesis, the inspection should include physical inspection and audit a sampling of records for both types of processing). This strategy, together with the classification of all profile classes upon completion of the inspection, will maximize the use of agency resources and avoid repeated visits to the same manufacturing site to cover different API profile classes referenced in subsequent applications. Any inspection of an API manufacturer should be recorded as a CGMP qualifying inspection.

Inspections should cover any specific APIs referenced in the assignment and any other representative APIs not inspected in the last two years. For foreign API firms, investigators should cover only APIs intended to be marketed or already marketed in the United States.

APIs selected for coverage should include those that are referenced in drug applications, are therapeutically significant, are intended for use in parenteral drug products, are difficult to manufacture, or are documented as having past compliance problems. However, this does not preclude the selection of less therapeutically significant APIs to evaluate specific APIs (or profile classes) not previously given in-depth coverage at the facility.

Investigators conducting API inspections should understand the general inspection strategy set forth in this program. Recognizing that API firms vary greatly in size, diversity of operations, and quality assurance systems, investigators should carefully plan their inspectional strategy at each firm. Further guidance on preparing an inspection strategy appears later.

Investigators should also review the firm's rationale for the point at which CGMPs begin, which is expected to vary by type of process (e.g., synthetic, fermentation, extraction, purification).

For an API inspection that is initiated by a pre-approval assignment, CP 7346.832, *Pre-Approval Inspections/Investigations*, inspection time should be reported under the appropriate program assignment codes referenced in both compliance programs based on the actual time spent in each program.

INSPECTION APPROACHES

This program provides two surveillance inspectional options: Full Inspection Option and Abbreviated Inspection Option. Either option may satisfy the biennial inspection requirement.

Full Inspection Option

The Full Inspection Option is a surveillance or compliance inspection which is meant to provide a broad and in-depth evaluation of the firm's conformity to CGMPs. The Full Inspection Option is an inspection of at least four of the six systems as listed in Part II and Appendix A of this program, one of which must be the Quality System.

A Full Inspection is appropriate:

- a. For an initial FDA inspection of a facility, or after a significant change in management or organizational procedures, such as might occur after a change in ownership.
- b. For a firm with a history of non-compliance or a recidivist firm whose ability to comply is short-lived. To determine if the firm meets this criterion, the District should utilize all information at its disposal, such as current and past inspection findings, results of sample analyses, complaints, recalls, and compliance actions.
- c. To evaluate if important changes have occurred in the firm's state of control by comparing current operations against the EIR for the previous Full Inspection (e.g., by conducting a Full Inspection at every fourth inspection cycle.) In addition to changes in management or ownership, the following types of changes are typical of those that warrant the Full Inspection Option:
 - i. New potential for cross-contamination arising through changes in processing or type of PIs using that equipment.
 - ii. Use of new technology requiring new expertise, significant equipment changes and/or additions, or new facilities.
- d. When District management or CDER specifically requests this option.
- e. To follow up on a Warning Letter or other regulatory action.

Abbreviated Inspection Option

The Abbreviated Inspection Option is a surveillance or compliance inspection which is meant to provide an efficient update evaluation of the firm's conformity to CGMPs. A satisfactory Abbreviated Inspection will provide documentation for continuing a firm in an acceptable CGMP compliance status. The Abbreviated Inspection Option is an inspection audit of at least two systems but not more than three 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.

An Abbreviated Inspection is appropriate when the Full Inspection Option is not warranted, including:

- a. To maintain surveillance over a historically compliant firm's activities and to provide input to the firm on maintaining and improving the CGMP level of assurance of quality of its APIs.
- b. When an intended Full Inspection finds objectionable conditions as listed in Part V of this program in one or more systems (a minimum of two systems must be completed) and District management and, as necessary, CDER Office of Compliance, concurs with reducing inspection coverage in order to expedite the issuance of a Warning Letter to correct violations.

Compliance Inspections

Compliance Inspections are inspections done "for-cause" and to evaluate or verify corrective actions after a regulatory action has been taken. 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 other 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 for the purpose of investigating a specific problem that has come to the attention of the agency and may not result in the coverage of systems as described in this program. The problem may be identified by a complaint, recall, or other indicator of defective API or poorly controlled process. Coverage of these problems may be assigned under other compliance programs or PACs; however, expansion of the coverage to a CGMP inspection is to be reported under this program. For-Cause Inspections may be assigned under this program as the need arises.

SELECTING SYSTEMS FOR COVERAGE

A complete description of each system and the areas for coverage are in Appendix A of this program. The selection of the system(s) for coverage and the relative depth or intensity of audit

coverage should take into consideration the relative significance of a particular system for the firm's specific operating conditions, history of previous coverage, and history of CGMP compliance. It is expected that a Full Inspection will not be conducted every two years at most firms. Districts should select different systems for inspection coverage as a cycle of Abbreviated Inspections is carried out to build comprehensive information on the firm's total manufacturing activities over time.

PREPARING THE INSPECTION STRATEGY

This guidance is in addition to that given in the *Investigations Operations Manual* (IOM).

1. Select two or more, as appropriate, systems for inspection coverage as guided by this program (see *Inspection Approaches*, above). *Appendix A* contains a detailed description of the inspection coverage to be given each system when selected for inspection.
2. Select significant APIs for inspection coverage, if not specified in the assignment. Significant APIs are those which utilize all the systems in the firm very broadly and/or use special manufacturing features, e.g., complex chemical synthesis, highly sensitizing material, material of an infectious nature, or a new chemical entity made under an approved drug application. Review the firm's FACTS listing, Drug Master Files (DMF) or A/NDA files.
3. If a CDER product or CGMP/regulatory reviewer (compliance officer) is assigned to participate as a member of the inspection team, the lead investigator is to brief them on the intended inspection strategy and explain their supporting role and responsibilities for the inspection. The lead investigator should consult the reviewer on any specific A/NDA chemistry, manufacturing and controls issues (whether pre-market or post-market) to be covered during the inspection.
4. Review the impurity profile for each API process to be covered during the inspection and compare these to the impurity profiles submitted in the application or DMF, if filed. (Investigators and Chemists should be particularly familiar with USP <1086> *Impurities in Official Articles*.) If the impurity profile has not been filed to CDER, review the guidance on establishing impurity profiles in ICH Q3A and Q3C.
5. Review any compendia monographs for the APIs to be inspected to verify conformity, as appropriate.
6. Before or during the inspection, determine if the firm has made process changes by comparing current operations against the EIR for the previous inspection. Also compare the current operations with those filed in the DMF or the drug application to determine whether the firm is complying with commitments made to the agency. (See also CP 7346.832 for conducting a pre-approval inspection of an API.) The following changes are typical of those that would warrant extensive coverage during the inspection:

- a. New potential for cross-contamination arising through changes in API processes or product-type lines, to include processing numerous APIs of varying toxicity in common equipment and/or facilities.
 - b. Use of new technology requiring new expertise, significantly new equipment or new facilities.
 - c. Changes in starting materials, intermediates, equipment, facilities, support systems, processing steps, packaging materials, or computer software, particularly those that are not referenced in the DMF or application.
7. For foreign firms, Division of Medical Products and Tobacco Inspections (DMPTI) will assist investigators in obtaining file information from the appropriate CDER reviewing division or compliance unit. Investigators may also request background information about the site assigned for inspection directly from the US Agent before the initiation of the inspection.

SPECIAL INSPECTION REPORTING INSTRUCTIONS:

Investigators should describe in the EIR their inspection coverage and findings in sufficient detail for further agency evaluation of the firm's state of control and conformance to CGMPs. ICH Q7 may be used as a guideline in describing coverage and any findings and deficiencies observed. However, do not reference specific ICH Q7 sections in the FDA 483 observations or in the EIR. The FDA 483, if issued, is to be organized into sections for each of the systems covered. In addition to the IOM format and information reporting requirements, all EIRs of API manufacturers must include:

1. A list of APIs manufactured (or categories of drugs, if many) along with the general manufacturing process for each (e.g., chemical synthesis, fermentation, extraction of botanical material).
2. For foreign API manufacturers, the names, titles, complete mailing address, telephone and fax number of the firm's U.S. Agent.
3. For foreign API manufacturers, a report of all APIs imported into the United States in the last two years, their consignees, and an estimate of the frequency and quantity of shipments to these consignees.
4. A description of each of the systems selected for coverage, (i.e., areas, processes, and operations), what was covered, who was interviewed, and what manufacturing activities were taking place during the inspection.
5. An explanation of the choice of APIs selected for coverage.
6. Any significant changes to a firm's packaging, labeling, product line, or processes, particularly those changes not properly filed, submitted, or reported in a DMF or A/NDA.

SPECIAL INSTRUCTIONS FOR FOREIGN DRUG INSPECTIONS

The Office of Medical Products and Tobacco Operations (OPMTO) schedules foreign inspections, makes travel arrangements for inspection teams, and resolves logistical problems. CDER's Office of Compliance, Division of International Drug Quality (DIDQ) receives and reviews all foreign establishment inspection reports, receives and reviews all foreign firms' responses to an FDA 483, and handles all correspondence regarding inspection outcomes with foreign firms. CDER/DIDQ maintains the complete file for each foreign drug facility.

Investigators should instruct management at foreign firms to submit their original written response to an FDA 483 directly to CDER's Office of Compliance, with a copy to the investigator. The original response with appropriate documentation should be submitted via email to

CDERICB@fda.hhs.gov

or to the following address:

Food and Drug Administration
Division of International Drug Quality
Office of Manufacturing and Product Quality
Center for Drug Evaluation and Research
Building 51, Room 4234
10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002
USA

Investigators and analysts are to submit their written comments to a foreign firm's response to their issued FDA 483 directly to DIDQ as soon as possible. After appropriate district office review and endorsement, all foreign establishment inspection reports will be promptly forwarded to FIT for review and final classification.

DIDQ will draft and coordinate the issuance of Warning Letters, Untitled Letters, and other correspondence to foreign firms. DIDQ will also recommend automatic detention of foreign firms/APIs, make recommendations to review units, and request follow-up inspections, as appropriate.

[end Part III]

PART IV - ANALYTICAL

API samples collected by the investigator for the purpose of evaluating quality are to be submitted to the appropriate servicing laboratory. A list of each analyzing laboratory for API testing is maintained in Compliance Programs 7356.002 and 7346.832. However, it should be noted that physical API samples are not required to support regulatory or administrative action against a violative firm or drug.

Forensic Chemistry Center (FCC) will request profile (also called “forensic” and “fingerprint”) samples of both foreign and domestic source APIs directly from the manufacturer. Investigators are to collect API samples for profile analysis only upon specific request for collection from FCC. Such requests will be made through DMPTPO. If an investigator is instructed to collect a profile sample, FCC will provide specific instructions as to method and amount of collection and shipping. FCC contact information is in Part VI, *Program Contacts*.

Prior to each foreign API site inspection, DMPTPO will provide FCC with the inspection dates, the investigator’s name, firm’s name, address, telephone number, fax number, FEI number, any related product and application numbers, and the name of the contact person. FCC will then directly request a sample from the firm as needed. FCC may contact the investigator to request their collection of any specific information. The inspection dates will provide FCC information so they can access FACTS to obtain the EIR coversheet.

FCC is responsible for API profile sample collection and analysis and will provide periodic reports of such analysis and assist CDER in evaluating this program’s effectiveness.

[end Part IV]

PART V - REGULATORY/ADMINISTRATIVE STRATEGY

An inspection report that documents that one or more systems is out of control should be classified OAI. Districts may recommend the issuance of a warning letter in accordance with the RPM. Normally, the issuance of a warning letter or the taking of other regulatory or administrative action should result in a classification of all profile classes as unacceptable. A CDER disapproval of a recommendation for warning letter or other regulatory action should result in a classification of all profile classes as acceptable.

A warning letter with a CGMP charge (i.e., 501(a)(2)(B) adulteration) involving a domestic API manufacturer requires CDER review and concurrence before issuance. See and follow *FDA Regulatory Procedures Manual* procedures for clearing warning letters and untitled letters.

A recommendation for regulatory action for API CGMP deficiencies is to cite the statute (501(a)(2)(B) or United States Code, 21 USC 351(a)(2)(B)) and not the finished pharmaceutical regulations at 21 CFR 210 and 211. A recommendation should also not cite to ICH Q7, but may use ICH Q7 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.

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 CDER; 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 NDA, USP, customer specifications, and label claims. See also Compliance Policy Guide (CPG) 7132.05. (Quality System)
3. Failure to comply with commitments in drug applications, including DMFs, 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. See also the revised CPG 7132c.08, *Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval*. (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 non-deliberate 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 carryover 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)

[end Part V]

PART VI - REFERENCES, ATTACHMENTS, AND PROGRAM CONTACTS

REFERENCES

Note regarding Guidance for Industry: Please review the guidance document posted at FDA's website to ensure you use the current version. FDA guidance documents, including ICH guidance, are here:

[\[http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm\]](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm)

1. ICH Guidance for Industry: Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients, August 2001
2. ICH Guidance for Industry: Q11 *Development and Manufacture of Drug Substances*
3. ICH Q3A *Impurities in New Drug Substances*
4. ICH Q3C *Impurities: Residual Solvents*, and appendices
5. Compliance Program 7356.002, Drug Manufacturing Inspections, and related programs
[\[http://www.fda.gov/ora/cpgm/#drugs\]](http://www.fda.gov/ora/cpgm/#drugs)
6. Compliance Policy Guide 490.100 (7132c.08), Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval
[\[http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/default.htm\]](http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/default.htm)
7. Compliance Policy Guide 420.400 (7132.05), Performance of Tests for Compendial Requirements on Compendial Products
[\[http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/default.htm\]](http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/default.htm)
8. The United States Pharmacopoeia / National Formulary (USP/NF) - available on-line through WebLERN
9. FDA Regulatory Procedures Manual
[\[http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/default.htm\]](http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/default.htm)

ATTACHMENTS – none.

PROGRAM CONTACTS

Center for Drug Evaluation and Research (CDER)

For questions relating to product quality, the application of CGMPs, and validation of active pharmaceutical ingredient processes contact:

Office of Manufacturing and Product Quality, Office of Compliance
Telephone: (301) 796-3120
Fax: (301) 827-8742

CDER maintains a list of contacts to help answer CGMP regulatory, technical, and program questions. This subject contact list is at <http://www.fda.gov/cder/dmpq/subjcontacts.htm>.

Office of Regulatory Affairs (ORA)

For questions on profile sampling of APIs: Food and Drug Administration

Forensic Chemistry Center (HFR-MA500)
Bulk Drug Group
6751 Steger Dr.
Cincinnati, Ohio 45237-3097
Telephone: (513) 679-2700, extension 185 or 181
Fax: (513) 679-2761

Office of Medical Products and Tobacco (OMPTO)

Division of Medical Products and Tobacco Program Operations
(OMPTO/DMPTPO)

Telephone: (301) 796-0358
Fax: (301) 827-9791

Office of Regulatory Science
(ORS)

Telephone: (301) 796-7057
Fax: (301) 827-9806

Office of Enforcement and Import Operations (OEIO)

Telephone: (301) 796-5270
Fax: (301) 827-3631

[end Part VI]

PART VII - CENTER RESPONSIBILITIES

Center responsibilities are as described in *Drug Manufacturing Inspections* Compliance Program 7356.002 and *Pre-Approval Inspection/Investigations* Compliance Program 7346.832

[end Part VII]

APPENDIX A: Description of Each System and Areas of Coverage

QUALITY SYSTEM

Assessment of the Quality System has two phases. The first phase is to evaluate whether the Quality 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 bulleted items, 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 the final API's, but may also include starting materials and intermediates. These areas may indicate deficiencies not only in this system but also in other systems that would warrant expansion of coverage. All areas under this system should be covered; however the actual depth of coverage may vary from the planned inspection strategy depending upon inspectional findings.

- Adequacy of staffing to ensure fulfillment of quality unit duties
- Periodic quality reviews as described in ICH Q7 Section 2.5, *Product Quality Review*; inspection audit coverage should include API types that are representative of manufacturing at this site; inspection audit should also examine some batch and data records associated with each API quality review to verify that firm's review was sufficiently complete; and, audit should confirm that firm has identified any trends and has corrected or mitigated sources of unacceptable variation.
- Complaint reviews (quality and medical): documented; evaluated; investigated in a timely manner; includes corrective action where appropriate. Determine whether pattern of complaints and records of internal rejection or reprocessing/reworking of API batches warrant expanding the inspection.
- Discrepancy and failure investigations related to manufacturing and testing: documented; evaluated; critical deviations investigated in a timely manner and expanded to include any related APIs and material; includes corrective action where appropriate.
- Change Control (including "process improvements"): documented; evaluated; approved; need for revalidation assessed.
- Returns/Salvages: assessment; investigation expanded where warranted; final disposition.
- Rejects: investigation expanded where warranted; corrective action where appropriate.
- System to release raw materials.
- Batches manufactured since last inspection to evaluate any rejections or conversions (i.e., from drug to non-drug use) due to processing problems.
- Reprocessing and/or reworking events are properly approved and evaluated for impact on material quality.
- Recalls (including any attempt to recover distributed API not meeting its specifications or purported quality), determine cause and corrective actions taken.
- Stability Failures: investigation expanded where warranted; disposition. Determine if stability data supports API retest or expiry dates and storage conditions.

- Validation: Status of validation/revalidation activities (e.g., computer, manufacturing process, laboratory methods), such as reviews and approvals of validation protocols and reports.
- Training/qualification of employees in quality control unit functions.

ICH Q7 references for **Quality System**:

- Section 2, *Quality Management*
- Section 13, *Change Control*
- Section 14, *Rejection and Reuse of Materials*
- Section 15, *Complaints and Recalls*
- Section 16, *Contract Manufacturers (including laboratories)*.

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 actual depth of coverage may vary from the planned inspection strategy depending upon inspectional findings.

1. Facilities

- Cleaning and maintenance.
- Facility layout, flow of materials and personnel for prevention of cross-contamination, including from processing of non-drug materials.
- Dedicated areas or containment controls for highly sensitizing materials (e.g., penicillin, beta- lactams, steroids, hormones, and cytotoxics).
- Utilities such as steam, gas, compressed air, heating, ventilation, and air conditioning should be qualified and appropriately monitored (note: this system includes only those utilities whose output is not intended to be incorporated into the API, such as water used in cooling/heating jacketed vessels).
- Lighting, sewage and refuse disposal, washing and toilet facilities.
- Control system for implementing changes in the building.
- Sanitation of the building including use of rodenticides, fungicides, insecticides, cleaning and sanitizing agents.
- Training and qualification of personnel.

2. Process Equipment

- Equipment installation, operational, performance qualification where appropriate.
- Appropriate design, adequate size and suitably located for its intended use.
- Equipment surfaces should not be reactive, additive, or absorptive of materials under process so as to alter their quality.
- Equipment (e.g., reactors, storage containers) and permanently installed processing lines should be appropriately identified.

- Substances associated with the operation of equipment (e.g., lubricants, heating fluids or coolants) should not come into contact with starting materials, intermediates, final APIs, and containers.
- Cleaning procedures and cleaning validation and sanitization studies should be reviewed to verify that residues, microbial, and, when appropriate, endotoxin contamination are removed to below scientifically appropriate levels.
- Calibrations using standards traceable to certified standards, preferably NIST, USP, or counterpart recognized national government standard-setting authority.
- Equipment qualification, calibration and maintenance, including computer qualification/validation and security.
- Control system for implementing changes in the equipment.
- Documentation of any discrepancy (a critical discrepancy investigation is covered under the Quality System).
- Training and qualification of personnel.

ICH Q7 references for **Facilities and Equipment System**:

- Section 4, *Buildings and Facilities*
- Section 5, *Process Equipment*
- Section 6, *Documentation and Records*

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 the final API, but may also incorporate starting materials and intermediates. 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 actual depth of coverage may vary from the planned inspection strategy depending upon inspectional findings.

- Training/qualification of personnel.
- Identification of starting materials, containers.
- Storage conditions.
- Holding of all material and APIs, including reprocessed material, under quarantine until tested or examined and released.
- Representative samples are collected, tested or examined using appropriate means and against appropriate specifications.
- A system for evaluating the suppliers of critical materials.
- Rejection of any starting material, intermediate, or container not meeting acceptance requirement.
- Appropriate retesting/reexamination of starting materials, intermediates, or containers.
- First-in / first-out use of materials and containers.
- Quarantine and timely disposition of rejected materials.
- Suitability of process water used in the manufacture of API, including as appropriate the water system design, maintenance, validation and operation.

- Suitability of process gas used in the manufacture of API (e.g., gas use to sparge a reactor), including as appropriate the gas system design, maintenance, validation and operation.
- Containers and closures should not be additive, reactive, or absorptive.
- Control system for implementing changes.
- Qualification/validation and security of computerized or automated process.
- Finished API distribution records by batch.
- Documentation of any discrepancy (a critical discrepancy investigation is covered under the Quality System).

ICH Q7 references for **Materials System**:

- Section 7, *Materials Management*
- Section 10, *Storage and Distribution*
- Section 4.3, *Water*
- Section 6, *Documentation and Records*

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 the final API, but may also incorporate starting materials and intermediates. 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 actual depth of coverage may vary from the planned inspection strategy depending upon inspectional findings.

- Training/qualification of personnel.
- Establishment, adherence, and documented performance of approved manufacturing procedures.
- Control system for implementing changes to process.
- Controls over critical activities and operations.
- Documentation and investigation of critical deviations.
- Actual yields compared with expected yields at designated steps.
- Where appropriate established time limits for completion of phases of production.
- Appropriate identification of major equipment used in production of intermediates and API.
- Justification and consistency of intermediate specifications and API specification.
- Implementation and documentation of process controls, testing, and examinations (e.g., pH, temperature, purity, actual yields, clarity).
- In-process sampling should be conducted using procedures designed to prevent contamination of the sampled material.
- Recovery (e.g., from mother liquor or filtrates) of reactants; approved procedures and recovered materials meet specifications suitable for their intended use.
- Solvents can be recovered and reused in the same processes or in different processes provided that solvents meet appropriate standards before reuse or commingling.

- API micronization on multi-use equipment and the precautions taken by the firm to prevent or minimize the potential for cross-contamination.
- Process validation, including validation and security of computerized or automated process
- Master batch production and control records.
- Batch production and control records.
- Documentation of any discrepancy (a critical discrepancy investigation is covered under the Quality System).

ICH Q7 references for **Production System**:

- Section 6, *Documentation and Records*
- Section 8, *Production and In-Process Controls*
- Section 12, *Validation*
- Section 18, *Specific Guidance for APIs Manufactured by Cell Culture / Fermentation*

See also Compliance Program 7356.0002M for additional inspection guidance on fermentation, extraction, and purification processes.

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 to the final API, but may also incorporate starting materials and intermediates. 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 actual depth of coverage may vary from the planned inspection strategy 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 APIs.
- 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 APIs.
- Adequate inspection (proofing) of incoming labeling.
- Use of lot numbers, destruction of excess labeling bearing lot/control numbers.
- Adequate separation and controls when labeling more than one batch at a time.
- Adequate expiration or retest dates on the label.
- Validation of packaging and labeling operations including validation and security of computerized process.
- Documentation of any discrepancy (a critical discrepancy investigation is covered under the Quality System).

ICH Q7 references for **Packaging and Labeling System**:

- Section 9, *Packaging and Identification Labeling of APIs and Intermediates*
- Section 17, *Agents, Brokers, Traders, Distributors, Repackers, and Relabellers* (applies to the handling of APIs after original site of manufacture and before receipt by the dosage manufacturer)

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 to the final API, but may also incorporate starting materials and intermediates. 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 actual depth of coverage may vary from the planned inspection strategy 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.
- Specifications, standards, and representative sampling plans.
- Validation/verification of analytical methods.
- Required testing is performed on the correct samples and by the approved or filed methods or equivalent methods.
- Documentation of any discrepancy (a critical discrepancy investigation is covered under the Quality System).
- 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 and disposition of unused data.
- Adherence to an adequate Out of Specification (OOS) procedure which includes timely completion of the investigation.
- Test methods for establishing a complete impurity profile for each API process (note: impurity profiles are often process-related).
- Adequate reserve samples; documentation of reserve samples examination.
- Stability testing program, including demonstration of stability indicating capability of the test methods.

ICH Q7 references for **Laboratory System**:

- Section 11, *Laboratory Controls*
- Section 6, *Documentation and Records*
- Section 12, *Validation*

ICH Q7 Sections 3, *Personnel*, and 6, *Documentation and Records*, apply to all systems. Section 19, *APIs for Use in Clinical Trials*, applies to APIs intended for the production of dosages solely for use in a clinical trial.

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 are required to maintain CGMPs and those selected for review should be included for inspection audit within the context of each of the above systems. Inspection of contract companies should be within the system for which the intermediate or API, or service is contracted and also include evaluation of their Quality System.

[end Appendix A]