
Contract Manufacturing Arrangements for Drugs: Quality Agreements Guidance for Industry

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)**

**November 2016
Pharmaceutical Quality/Manufacturing Standards (CGMP)**

Contract Manufacturing Arrangements for Drugs: Quality Agreements Guidance for Industry

Additional copies are available from:

*Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration*

*10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002*

Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353

Email: druginfo@fda.hhs.gov

*<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>
and/or*

*Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration*

*10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002*

Phone: 800-835-4709 or 240-402-8010

Email: ocod@fda.hhs.gov

*<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>
and/or*

*Policy and Regulations Staff, HFV-6
Center for Veterinary Medicine
Food and Drug Administration*

7519 Standish Place, Rockville, MD 20855

<http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/default.htm>

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)**

**November 2016
Pharmaceutical Quality/Manufacturing Standards (CGMP)**

TABLE OF CONTENTS

I.	INTRODUCTION.....	1
II.	DEFINING THE WHO AND WHAT OF CONTRACT MANUFACTURING	2
III.	RESPONSIBILITIES OF PARTIES INVOLVED IN CONTRACT MANUFACTURING	3
IV.	DOCUMENTING CGMP ACTIVITIES IN QUALITY AGREEMENTS.....	5
	A. What Is a Quality Agreement?	6
	B. Elements of a Quality Agreement.....	6
	1. <i>Manufacturing Activities.....</i>	<i>7</i>
	2. <i>Change Control Associated With Manufacturing Activities</i>	<i>10</i>
V.	ILLUSTRATIVE SCENARIOS	11
	A. Owners and Contract Facilities Are Both Responsible for CGMP	11
	B. CGMPs Apply to all Contract Facilities, Including Analytical Testing Laboratories.....	12
	C. Owners and Contract Facilities Perform Change Control Activities	13
VI.	RECOMMENDATIONS.....	13

Contract Manufacturing Arrangements for Drugs: Quality Agreements Guidance for Industry¹

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance describes FDA's current thinking on defining, establishing, and documenting manufacturing activities of the parties involved in contract drug manufacturing subject to current good manufacturing practice (CGMP) requirements. In particular, we describe how parties involved in contract drug manufacturing can use quality agreements to delineate their manufacturing activities to ensure compliance with CGMP.

For purposes of this guidance, we use certain terms with the following specific meanings:

- *Current Good Manufacturing Practice (CGMP)* refers to requirements in the Federal Food, Drug, and Cosmetic Act (FD&C Act), section 501(a)(2)(B), for all drugs and active pharmaceutical ingredients (APIs). For finished human and animal drugs, the term includes applicable requirements under 21 CFR parts 210 and 211. For biologics, the term includes additional applicable requirements under 21 CFR parts 600-680.
- *Commercial manufacturing* refers to manufacturing processes that result in a drug or drugs intended to be marketed, distributed, or sold.
- *Commercial manufacturing* does not include research and development activities, manufacturing of material for investigational new drug studies (e.g., clinical trials, expanded access), or manufacturing of material for veterinary investigational drugs. Although this guidance does not explicitly apply to the manufacture of investigational, developmental, or clinical trial materials, FDA believes that quality agreements can be extremely valuable in delineating the activities of all parties involved in contract research and development arrangements. Many of the principles described in this guidance could be applied in pre-commercial stages of the pharmaceutical life cycle.

¹ This guidance has been prepared by the Office of Pharmaceutical Quality and the Office of Compliance in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research, the Center for Veterinary Medicine, and the Office of Regulatory Affairs at the Food and Drug Administration.

Contains Nonbinding Recommendations

- *Manufacturing* includes processing, packing, holding, labeling operations, testing, and quality unit operations.
- A *manufacturer* is an entity that engages in CGMP activities, including implementation of oversight and controls over the manufacture of drugs to ensure quality.²
- *Quality unit* is defined as synonymous with the term *quality control unit*.³

This guidance covers commercial manufacturing of the following categories of drugs: human drugs, veterinary drugs, certain combination products, biological and biotechnology products, finished products, APIs, drug substances, in-process materials, and drug constituents of combination drug/device products.⁴ This guidance does not cover the following types of products: Type A medicated articles and medicated feed, medical devices, dietary supplements, or human cells, tissues, or cellular or tissue-based products regulated solely under section 361 of the Public Health Service Act and 21 CFR part 1271.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. DEFINING THE WHO AND WHAT OF CONTRACT MANUFACTURING

This guidance describes how contract manufacturing operations fit within the larger scheme of pharmaceutical quality systems. It also presents the Agency's current thinking on the roles and manufacturing activities of the parties involved in contract manufacturing arrangements. Specifically, this guidance addresses the relationship between owners and contract facilities. For purposes of this guidance, we define *owners* as manufacturers of APIs, drug substances, in-process materials, finished drug products, including biological products, and combination products. The term *owner* does not apply to retail pharmacies, drug stores, supermarkets, discount warehouse stores, or other retailers who purchase finished drug products to sell over the counter as a store brand. For purposes of this guidance, we define *contract facilities* as parties that perform one or more manufacturing operations on behalf of an owner or owners.⁵

² See section 501 of the FD&C Act, as amended by the Food and Drug Administration Safety and Innovation Act (Public Law 112-144, title VII, section 711).

³ For *quality control unit*, see 21 CFR 210.3.

⁴ Combination product manufacturers can apply this guidance to their quality agreements because they are subject to requirements under 21 CFR part 211 and/or 21 CFR part 820 (see 21 CFR 4.3). In addition to facilitating compliance with requirements under 21 CFR part 211, manufacturers can use quality agreements with contract facilities to demonstrate compliance, in part, with 21 CFR 820.50 (purchasing controls) and with 21 CFR 820.80(b) (receiving acceptance activities) for combination products.

⁵ A contract facility may also be an owner depending on its role (e.g., when the contract facility is using a subcontractor).

Contains Nonbinding Recommendations

Drug manufacturing encompasses many discrete operations and activities. One manufacturer may perform all operations and activities or may engage an outside party or parties to perform some or all of the operations and activities under contract. Contract facilities perform a variety of manufacturing operations and activities, including but not limited to:

- Formulation
- Fill and finish
- Chemical synthesis
- Cell culture and fermentation, including for biological products
- Analytical testing and other laboratory services
- Packaging and labeling
- Sterilization or terminal sterilization

However, agreements between owners and contract facilities sometimes do not clearly define the CGMP-related roles and manufacturing operations and activities of each of the parties. When all parties clearly understand their CGMP-related roles and manufacturing responsibilities, the owners who use contract facilities, contract facilities that provide services to owners, and, ultimately, patients who take the drugs manufactured under these arrangements may benefit in many ways. Contracting can enhance speed and efficiency, provide technological expertise, and expand capacity.

We encourage entities that engage in manufacturing related solely to drug distribution (e.g., distributors, brokers, private label distributors, own label distributors) to follow the recommendations in this guidance document, as appropriate. Our focus here, however, is on the roles and manufacturing activities of the owner and contract facility.

III. RESPONSIBILITIES OF PARTIES INVOLVED IN CONTRACT MANUFACTURING

Each party engaged in the manufacture of a drug is responsible for ensuring compliance with CGMP for the manufacturing activities it performs.⁶ For both owners and contract facilities that conduct manufacturing operations, CGMP “includes the implementation of oversight and controls over the manufacture of drugs to ensure quality, including managing the risk of and establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished drug products.”⁷ Drugs not manufactured in compliance with CGMP are adulterated.⁸

The FD&C Act also prohibits any person from introducing or delivering for introduction an adulterated or misbranded drug into interstate commerce.⁹ In addition, it prohibits anyone from the “doing of any ... act with respect to, a ... drug ... if such act is done while such article is held

⁶ Section 501(a)(2)(B) of the FD&C Act; 21 CFR parts 210 and 211; and 21 CFR part 600.

⁷ Section 501 of the FD&C Act as amended by the Food and Drug Administration Safety and Innovation Act (Public Law 112-144, Title VII, section 711).

⁸ Section 501(a)(2)(B) of the FD&C Act.

⁹ Section 301(a) of the FD&C Act.

Contains Nonbinding Recommendations

for sale ... after shipment in interstate commerce and results in such article being adulterated or misbranded.”¹⁰

FDA’s regulations recognize that owners commonly use contract facilities to perform some drug manufacturing activities.¹¹ When an owner uses a contract facility, the owner’s quality unit is legally responsible for approving or rejecting drug products manufactured by the contract facility, including for final release.¹² The regulations require that the quality unit’s responsibilities and procedures be in writing and that they be followed.¹³

Owners can use a comprehensive quality systems model to help ensure compliance with CGMP. A comprehensive quality systems model anticipates that many owners will use contract facilities and calls for quality agreements between owners and contract facilities. Quality agreements should clearly describe the materials or services to be provided, quality specifications, and communication mechanisms between the owner and contract facility. See guidance for industry *Quality Systems Approach to Pharmaceutical CGMP Regulations*.¹⁴

Owners and contract facilities can review FDA guidance documents for recommendations on achieving compliance with CGMP. Various FDA guidance documents describe how quality management principles relate to contract manufacturing operations, including some of the roles and manufacturing activities of contract manufacturing parties.¹⁵

The following three ICH guidances for industry contain relevant and valuable CGMP recommendations with respect to contract manufacturing arrangements:

- *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*
- *Q9 Quality Risk Management*
- *Q10 Pharmaceutical Quality System*

ICH guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* recommends that owners evaluate contract facilities to ensure that contractor sites comply with CGMP for specific operations.¹⁶ It also recommends that owners have approved written agreements with contractors that define the manufacturing responsibilities in detail, including the quality measures, of each party. The written agreements should also define considerations for subcontracting; describe how changes to processes, equipment, methods, and specifications will be managed; and permit the owner to audit its contractor’s facilities for compliance with CGMP.

¹⁰ Section 301(k) of the FD&C Act.

¹¹ 21 CFR 200.10(b) and 211.22(a).

¹² Ibid.

¹³ 21 CFR 211.22(d).

¹⁴ We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

¹⁵ See, e.g., guidance for industry *Cooperative Manufacturing Arrangements for Licensed Biologics*.

¹⁶ In ICH Q7, the term *company* is used rather than *owner* and is used to refer to an API manufacturer.

Contains Nonbinding Recommendations

ICH guidance for industry *Q9 Quality Risk Management* offers a systematic approach to quality risk management as part of an effective quality system. It discusses quality risk management principles such as risk assessment, risk communication, and risk review and provides examples of tools that can be used to make effective and efficient risk-based decisions in, for example, auditing and arranging quality agreements with contract manufacturers.

ICH guidance for industry *Q10 Pharmaceutical Quality System* states that, as part of a pharmaceutical quality system, the owner is ultimately responsible for ensuring that “processes are in place to assure the control of outsourced activities and quality of purchased materials.”¹⁷ It indicates that these processes should incorporate quality risk management and include the following critical activities:

- Assessing the suitability and competence of potential contractors before outsourcing operations or selecting material suppliers. This could be accomplished through audits, material evaluations, or other qualification criteria.
- Defining the manufacturing responsibilities and communication processes for quality-related activities of the involved parties. For outsourced activities, these should be in a written agreement.
- Monitoring and reviewing the performance of the contract facility and identifying and implementing any needed improvements.
- Monitoring incoming ingredients and materials to ensure they are from approved sources using the agreed-upon supply chain.

FDA encourages parties engaged in contract manufacturing to implement quality management practices. This guidance is intended to build upon the quality risk management principles and recommendations outlined above and to illustrate key points in developing and executing quality agreements that describe and support contract manufacturing arrangements.

IV. DOCUMENTING CGMP ACTIVITIES IN QUALITY AGREEMENTS

If an owner employs a contract facility for all or part of the manufacturing (including processing, packing, holding, or testing) of a drug or drug product, the owner’s quality unit is responsible for approving or rejecting the contract facility’s product or service.¹⁸ The contract facility is also required to comply with statutory CGMP and applicable CGMP regulations, including requirements for its quality unit.¹⁹ CGMP regulations require that quality unit activities and procedures be in writing, and that these procedures be followed.²⁰

Implementing a written quality agreement can facilitate compliance with CGMP and, in particular, with 21 CFR 211.22(d), which states that quality unit activities and procedures should be in writing. FDA recommends that owners and contract facilities establish a written quality agreement to describe their respective CGMP-related roles, responsibilities, and activities in drug

¹⁷ In ICH Q10, the term *company* is used rather than *owner*.

¹⁸ Section 501(a)(2)(B) of the FD&C Act; 21 CFR 211.22(a).

¹⁹ 21 CFR 210.2(b); 21 CFR 211.22(a).

²⁰ 21 CFR 211.22(d).

Contains Nonbinding Recommendations

manufacturing. It is important to note that quality agreements cannot be used to delegate statutory or regulatory responsibilities to comply with CGMP. The following sections describe the Agency's current thinking regarding the documentation of agreed-upon manufacturing activities in a quality agreement, as well as the basic elements of a quality agreement.

A. What Is a Quality Agreement?

A quality agreement is a comprehensive written agreement between parties involved in the contract manufacturing of drugs that defines and establishes each party's manufacturing activities in terms of how each will comply with CGMP. In general, the quality agreement should clearly state which party — the owner or the contract facility or both — carries out specific CGMP activities. It should cover activities mentioned in section 501(a)(2)(B) of the FD&C Act and, as applicable, those in 21 CFR parts 210, 211, 600-680, 820, and 1271, as well as all other applicable statutory or regulatory requirements. Representatives from each party's quality unit and other relevant stakeholders should participate actively in the drafting of quality agreements.

Quality agreements should not cover general business terms and conditions such as confidentiality, pricing or cost issues, delivery terms, or limits on liability or damages. FDA recommends that quality agreements be separate documents, or at least severable, from commercial contracts such as master services agreements or supply agreements. Quality agreements may be reviewed during inspections.²¹

B. Elements of a Quality Agreement

A quality agreement describes the owner's and the contract facility's roles and manufacturing activities under CGMP. A well-written quality agreement will use clear language. It will define key manufacturing roles and responsibilities. It will establish expectations for communication, providing key contacts for both parties. It will specify which products and/or services the owner expects from the contract facility and who has final approval for various activities. Most quality agreements contain the following sections:

- Purpose/Scope — to cover the nature of the contract manufacturing services to be provided
- Definitions — to ensure that the owner and contract facility agree on precise meaning of terms in the quality agreement
- Resolution of disagreements — to explain how the parties will resolve disagreements about product quality issues or other problems
- Manufacturing activities — to document quality unit and other activities associated with manufacturing processes as well as control of changes to manufacturing processes
- Life cycle of, and revisions to, the quality agreement

The owner may consider including the contract facility's established processes and procedures as part of the quality agreement (for example, by incorporating certain standard operating

²¹ See section 704 of the FD&C Act.

Contains Nonbinding Recommendations

procedures by reference). Doing so could reduce the risk of misinterpretation or error during manufacturing. The quality agreement should explain how the contractor will report manufacturing deviations to the owner, as well as how deviations will be investigated, documented, and resolved in compliance with CGMP. Quality agreements should state that manufacturing services provided by contract facilities (including laboratories) will comply with CGMP.

From a CGMP perspective, manufacturing activities are the most important element in a quality agreement. The most critical pieces are quality and change control, as described in the following sections.

1. Manufacturing Activities

Quality agreements may document each party's roles and manufacturing activities with a variety of formats — charts, matrices, narratives, or a combination of these. Regardless of the format, a quality agreement should clearly document which party is responsible for specific activities. No party to a quality agreement may delegate any of its responsibilities to comply with CGMP through the quality agreement or any other means. The quality agreement should cover all of the activities for ensuring compliance with CGMP. Depending on the scope of the contract manufacturing services to be provided, the quality agreement should indicate whether the owner or contract facility (or both) will handle specific activities related to each of the following topics:

a. Quality unit activities

The section of a quality agreement that addresses each party's quality unit activities should define in detail how the parties will work together to ensure that products are manufactured in compliance with CGMP. Note that assigning quality control or other activities to either the owner or contract facility in the quality agreement does not relieve either party from compliance with applicable CGMP requirements.

In particular, this section of the quality agreement should be clear with respect to product release. Contract facilities are responsible for approving or rejecting the product or results of their manufacturing operations (e.g., test results, finished dosage forms, or in-process materials).²² In addition, owners are responsible for approving or rejecting drugs manufactured by the contract facility,²³ including for final release. In all cases, the owner must not introduce or deliver into interstate commerce, or cause to be introduced or delivered into interstate commerce, any drugs that are adulterated or misbranded.²⁴

Within its quality unit activities, a quality agreement should describe how and when the owner and contract facility will communicate with each other, both verbally and in writing. This includes identifying appropriate contact personnel within the owner's and contract facility's organization.

²² 21 CFR 211.22(a).

²³ Section 501(a)(2)(B) of the FD&C Act; 21 CFR 211.22(a).

²⁴ See section 301(a) of the FD&C Act.

Contains Nonbinding Recommendations

Quality agreements should also cover audits, inspections, and communication of findings. The agreement should allow owners to evaluate and audit contract facilities to ensure CGMP compliance for specific operations. This provision should cover both routine quality audits and for-cause audits. The agreement should also set owner and contract facility expectations regarding FDA inspections (pre-approval, routine surveillance, and for-cause) with consideration for the nature of the products to be manufactured and/or services to be provided. It should include the parties' agreed-upon provisions for communicating inspection observations and findings, as well as relevant FDA actions and correspondence.

Because contract facilities often provide services to multiple owners, the quality agreement should address when, how, and what information the contractor will report to owners about objectionable conditions observed during inspections and audits of the contract facility.

b. Facilities and equipment

This section of a quality agreement should identify the specific site(s) where the contract facility will perform manufacturing operations, including the address of and specific services to be provided at each site. It should indicate which party will be validating processes and qualifying and maintaining equipment and applicable systems relevant to the contracted operations. These include information technology and automated control systems, environmental monitoring and room classification, utilities, and any other equipment and facilities that must be maintained to perform the contracted manufacturing operations in compliance with CGMP. The agreement also should identify which party will approve equipment validation, qualification, and maintenance activities. In addition, it should indicate how the parties will communicate information about preventing cross-contamination and maintaining traceability when a contract facility processes drugs for multiple owners.

c. Materials management

This section of a quality agreement should indicate which party will establish specifications for components as well as which party will establish processes for auditing, qualifying, and monitoring component suppliers. It should also identify which party will conduct required sampling and testing in compliance with CGMP. This section of the quality agreement should address how the parties will ensure appropriate inventory management, including labeling, label printing, inventory reconciliation, and product status identification (e.g., quarantine). The agreement should address how the contract facility will prevent mix-ups and cross-contamination. FDA does not expect the agreement to contain a complete description of the supply chain for each component. However, the agreement should define responsibility for physical control of materials at different points in the manufacturing process. For example, the quality agreement should cover responsibilities for proper conditions for storing and transporting or shipping materials. It should define each party's roles in storage and transport — whether from the contract facility back to the owner or to another contract facility for further operations. This includes defining activities for monitoring or validating shipping conditions as appropriate.

Contains Nonbinding Recommendations

d. Product-specific considerations

A comprehensive quality agreement may address specific considerations related to individual products. The owner and contract facility might opt to include this information in an appendix, or directly in the body of the quality agreement. In either case, if included, this section of the quality agreement should include the parties' expectations of each other regarding:

- Product/component specifications
- Defined manufacturing operations, including batch numbering processes
- Responsibilities for expiration/retest dating, storage and shipment, and lot disposition
- Responsibilities for process validation, including design, qualification, and ongoing verification and monitoring
- Provisions to allow owner personnel access to the contract facility when appropriate

The quality agreement also should indicate how owners will transfer knowledge, such as product and process development information, to contract facilities to ensure a drug can be manufactured in compliance with CGMP, and conversely how contract facilities should share with owners product quality information gained throughout the product life cycle. This applies to knowledge about all drugs, including drugs subject to an approved application (e.g., new drug application) and nonprescription drug products marketed under an over-the-counter drug monograph.

Owners that hold an approved drug application should be aware of application and approval requirements that could affect manufacturing activities. Both parties to a quality agreement should share relevant information to ensure compliance with CGMP and other applicable requirements of the FD&C Act.

e. Laboratory controls

The owner and contract facility should both have access to adequate laboratory facilities for testing of their drugs. A quality agreement will help each party meet this need by defining roles and responsibilities for laboratory controls. We recommend the following elements:

- Procedures delineating controls over sampling and testing samples
- Protocols and procedures for communicating all laboratory test results conducted by contract facilities to the owner for evaluation and consideration in final product disposition decisions
- Procedures to verify that both owner and contract facilities accurately transfer development, qualification, and validation methods when an owner uses a contract facility for laboratory testing
- Routine auditing procedures to ensure that a contract facility's laboratory equipment is qualified, calibrated, and maintained in a controlled state in accordance with CGMP

Contains Nonbinding Recommendations

- Designation of responsibility for investigating deviations, discrepancies, failures, out-of-specification results,²⁵ and out-of-trend results in the laboratory, and for sharing reports of such investigations

f. Documentation

The quality agreement should define expectations between the contract facility and the owner to review and approve documents. It also should describe how changes may be made to standard operating procedures, manufacturing records, specifications, laboratory records, validation documentation, investigation records, annual reports, and other documents related to products or services provided by the contract facility. The quality agreement should also define owners' and contract facilities' roles in making and maintaining original documents or true copies in accordance with CGMP. It should explain how those records will be made readily available for inspection.

The quality agreement also should indicate that electronic records will be stored in accordance with CGMP and will be immediately retrievable during the required record-keeping time frames established in applicable regulations.

2. *Change Control Associated With Manufacturing Activities*

Either an owner or a contract facility may initiate changes to processes, equipment, test methods, specifications, and other contractual requirements. Both parties should discuss changes and address them in the quality agreement. There are some changes that owners should review and approve before they are implemented and other changes contractors may implement without notifying the owner. How all changes are managed should be outlined in the agreement, including allocation of responsibilities for conducting validation activities as needed before implementing changes. Additionally, both parties should be aware of those changes that need to be submitted to FDA in a supplement or annual report. The owner and contract facility should carefully consider and agree on the types of changes to report to each other and to FDA and the need for approval from each party's quality unit and FDA, as applicable. The quality agreement should address expectations for reporting and approving changes to the following:

- Components and/or their suppliers
- Establishment locations
- Manufacturing processes
- Products or product types that use the same production line, equipment train, or facility
- Testing procedures
- Major manufacturing equipment
- Shipping methods
- Lot numbering scheme
- Container closure systems
- Tamper evidence features

²⁵ Refer to the guidance for industry *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production*.

Contains Nonbinding Recommendations

- Product distribution

Various unexpected events, such as manufacturing deviations, complaints, product recalls, adverse event reports, master label changes, field alert reports, and biological product deviation reports, may necessitate changes to processes and procedures. Process improvement projects, process capability analyses, and trending reports may also necessitate changes to processes and procedures. The quality agreement should include the owner's and contract facility's expectations for reporting and communication in case of unexpected events and related changes.

V. ILLUSTRATIVE SCENARIOS

The following hypothetical scenarios illustrate common problems in contract manufacturing arrangements and depict ways in which both owners and contract facilities can affect product quality. These scenarios also demonstrate FDA's current thinking regarding potential ways to resolve problems. The examples provided are not intended to encompass all drug manufacturing problems related to arrangements between owners and contract facilities. Rather, they provide industry and other stakeholders with patterns FDA investigators frequently encounter and analyses of the facts within these patterns.

A. Owners and Contract Facilities Are Both Responsible for CGMP

Case 1: Facilities and Equipment Maintenance and Upkeep at Contract Facility

An FDA inspection of a contract facility that manufactures an injectable drug product for an owner reveals significant objectionable conditions at the contract facility. Most of the objectionable conditions relate to deficient maintenance of facilities and equipment used to manufacture the injectable drug product. Equipment is broken. Pipes are tarnished, and seals are leaking. In addition, the facility design does not adequately prevent contamination. A quality agreement between the contract facility and the owner states that the owner is responsible for upgrades and maintenance of the facilities and equipment used to manufacture the owner's product. The owner has failed to provide upgrades and perform maintenance, and the contract facility continues to manufacture the product under non-CGMP conditions with risk of contamination.

Case 2: Documenting Steps in the Manufacturing Process

A contract facility is manufacturing a prescription drug product for an owner. FDA has approved an application from the owner for this drug. On inspection, FDA observes that the contract facility's batch records do not accurately reflect the actual manufacturing process because the batch records do not document the addition of reclaimed powder. Despite the fact that the batch records are inaccurate and are therefore not compliant with CGMP, the contract facility claims that its batch records comply with expectations set out in the quality agreement with the owner.

In the cases described above, the owners and contract facilities appear to be in violation of CGMP. A quality agreement cannot exempt owners or contract facilities from statutory or

Contains Nonbinding Recommendations

regulatory responsibilities to comply with applicable CGMP, regardless of whether the quality agreement specifically discusses those CGMP requirements. In case 1, the contract facility violates CGMP requirements by continuing to manufacture on outdated or poorly designed equipment, even though the quality agreement says that the owner is responsible for maintenance and upkeep of the equipment. In case 2, the contract facility violates CGMP by using a batch record that does not accurately reflect the manufacturing process, even though the batch record is consistent with what was set out in the quality agreement.

At the same time, the owner remains responsible for ensuring its products are made in compliance with CGMP even when a quality agreement assigns a particular manufacturing activity to the contract facility. After finding problems at a contract facility, such as the ones described in the cases above, FDA might determine that it is appropriate to inspect the owner. The owner could also be in violation of CGMP related to its failure to oversee the contract facility's manufacturing activities.

B. CGMPs Apply to all Contract Facilities, Including Analytical Testing Laboratories

Case 3: Unreliable Data in Laboratory Records and Test Results

In this scenario, an owner contracts with a facility for analytical testing services. The contract facility repeatedly reports passing results in its CGMP records when actual analyses indicated failures. The contract facility also fails to report accurate results to the owner, who is the finished drug product manufacturer. When FDA inspects the owner, it finds that despite having a written procedure requiring a site audit of contract facilities every 2 years, the owner has not audited the analytical testing facility.

Case 4: Contracted Analytical Testing Laboratory and Method Validation

An owner contracts with a facility to perform stability testing and other analyses of its newly approved drug. FDA approval and a quality agreement with the owner require the drug to be manufactured using these processes, which are described in the owner's new drug application (NDA). The contract facility uses an analytical method contained in the NDA but gets several out-of-specification results. Also, the facility's duplicate sample analyses occasionally point to possible unacceptable variations in drug concentration. The facility investigates the varying results and concludes that the failures are related to the sample preparation techniques but does not clearly identify the problem. Despite this, the contract facility continues to use the noncompliant method to test the product. When FDA inspects the contract facility, it finds that the facility failed to fully investigate the problems and implement corrective actions. The contract facility claims that because it used the owner's analytical method as specified in the product application, it is not responsible for investigating and implementing corrections related to it.

In both of the cases above, FDA might conclude that the contract facilities are responsible for violating CGMP applicable to the laboratory activities they perform. FDA could also conclude

Contains Nonbinding Recommendations

that the owners are responsible for CGMP violations. Analytical testing laboratories are responsible for operating in compliance with CGMP regardless of quality agreements they may have with owners. They must employ adequate controls to ensure that data and test results are reliable and maintained in accordance with CGMP requirements. It is the owner's responsibility to review this information from the contract facility to decide whether to approve or reject product for release and distribution.²⁶

No matter who tests the products, the owners' quality units are ultimately responsible for ensuring that the products are manufactured in accordance with CGMP. A quality agreement does not change that. FDA could cite the owners in cases 3 and 4 further for failing to evaluate, qualify, audit, and monitor their contract facilities.

C. Owners and Contract Facilities Perform Change Control Activities

Case 5: Approving or Rejecting Changes That Affect Product Quality and CGMP Compliance

A contract facility informed the owner about obvious powder segregation issues. The contract facility had attempted to correct the problem by making changes to the equipment, but then determined that the issues could not be fixed without process redesign and component changes. Under their quality agreement, the contract facility could not implement these changes without the owner's approval. The owner refused to approve the recommended changes, so the contract facility continued manufacturing the product using the flawed process and is therefore not compliant with CGMP.

Case 5 illustrates the responsibilities of both owners and contract facilities when change control issues are in question. Owners may be reluctant to approve changes recommended by contract facilities, even if changes are necessary to continue manufacturing the drug in compliance with CGMP.

VI. RECOMMENDATIONS

Owners and contract facilities can draw on quality management principles to carry out the complicated process of contract drug manufacturing by defining, establishing, and documenting their activities in drug manufacturing operations, including processing, packing, holding, labeling operations, testing, and quality control operations. Accordingly, FDA recommends that owners and contract facilities implement written quality agreements as tools to delineate manufacturing activities for ensuring compliance with CGMP.

²⁶ See, for example, §§ 211.22(a), 211.68, 211.180, 211.188, and 211.194(a).