Guidance for Industry

Contract Manufacturing Arrangements for Drugs: Quality Agreements

DRAFT GUIDANCE

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Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)

May 2013
Current Good Manufacturing Practices (CGMP)

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TABLE OF CONTENTS

Guidance for Industry[1]

Contract Manufacturing Arrangements for Drugs: Quality Agreements

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance describes our current thinking on defining, establishing, and documenting the responsibilities of each party (or all parties) involved in the contract manufacturing of drugs subject to Current Good Manufacturing Practice (CGMP). In particular, we describe how parties involved in the contract manufacturing of drugs can utilize Quality Agreements to delineate their responsibilities and assure drug quality, safety, and efficacy. This guidance applies to the commercial manufacturing[2] of Active Pharmaceutical Ingredients (APIs or drug substances, or their intermediates), finished drug products, combination products, and biological drug products.[3] [4] For the purposes of this guidance, the term "manufacturing" includes processing, packing, holding, labeling operations, testing, and operations of the Quality Unit.

[1] This draft guidance has been prepared by the Office of Manufacturing and Product Quality in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER), the Center for Veterinary Medicine (CVM), and the Office of Regulatory Affairs (ORA) at the Food and Drug Administration (FDA).

[2] In this guidance, the term *commercial manufacturing* refers to manufacturing processes that result in *commercial product*, i.e., drug that is intended to be marketed, distributed, and sold or intended to be sold. For purposes of this guidance, the term *commercial manufacturing* does not include research and development activities or the manufacture of material for clinical trials or treatment Investigational New Drugs (INDs), or for veterinary investigational files (INADs or JINADs).

[3] This guidance covers the following categories of drugs: human drugs, veterinary drugs, certain combination products, biological and biotechnology products, finished products, active pharmaceutical ingredients (APIs or drug substances, or their intermediates), and drug constituents of combination drug/device products. This guidance does not cover the following types of products: Type A medicated articles and medicated feed, medical devices, dietary supplements, or human tissues intended for transplantation regulated under section 361 of the Public Health Service Act.

[4] Quality Agreements described in this guidance should also be used by Owners of combination products as they are subject to requirements under 21 CFR 211, 21 CFR 820, or both (see 21 CFR 4.3). In addition to facilitating compliance with requirements under 21 CFR 211, Quality Agreements with Contracted Facilities would also be appropriate for demonstrating compliance, in part, with 21 CFR 820.50 (Purchasing Controls) and with 21 CFR 820.80(b) (Receiving Acceptance Activities), for the combination product..

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidance documents 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 guidance documents means that something is suggested or recommended, but not required.

II. DEFINING THE "WHO" AND "WHAT" OF CONTRACT MANUFACTURING

Manufacturing pharmaceutical products or materials may involve many discrete unit operations and activities. The entire process may be conducted by the owner of the drug, or, alternatively, the owner may engage an outside party or parties to complete the entire manufacturing process, or one or more discrete operations, under contract. In this document, when discussing the roles and responsibilities of the parties to such contractual relationships, we will refer to the party that introduces (or causes the introduction of) a drug into interstate commerce as the *Owner* of the drug, whether such drug is covered by a marketing application/license or not.[5] In this guidance, outside entities performing manufacturing operations for the product Owner are called *Contracted Facilities*.

Some of the manufacturing operations Contracted Facilities perform for Owners include, but are not limited to: (1) formulation; (2) fill and finish; (3) chemical synthesis; (4) cell culture and fermentation, including biological products; (5) analytical testing and other laboratory services; and (6) packaging and labeling. Owners may benefit from using contracted facilities in many ways, including enhanced speed and efficiency in specific processes, expertise in a specific technology, and expanded capacity. In all cases, the Owner is responsible for assuring that drugs introduced for interstate commerce are neither adulterated nor misbranded as a result of the actions of their selected Contracted Facilities. All Contracted Facilities must assure compliance with applicable Current Good Manufacturing Practices for all manufacturing, testing or other support operations performed to make a drug(s) for the Owner.

This guidance describes how contract manufacturing operations fit within the larger scheme of pharmaceutical quality systems and presents the Agency's current thinking on the roles and responsibilities of entities involved in contract manufacturing arrangements.

III. ESTABLISHING RESPONSIBILITIES OF CONTRACT MANUFACTURING

A. Statutory and Regulatory Framework

Under section 301(a) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 301(a)), manufacturers are liable for introducing or causing the introduction of adulterated or misbranded drugs into interstate commerce. Under section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B)), a drug is adulterated if "the methods used in, or the facilities or controls

[5] As used in this guidance, the term "Owner" does not apply to entities such as retail pharmacies or drug stores, supermarkets, discount warehouse stores, or other entities who are primarily retailers and who purchase from a registered drug manufacturer quantities of an OTC finished drug product labeled for sale with the retailer's store brand.

used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this chapter as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess." .

Additionally, drug products may be deemed misbranded under a variety of provisions (section 502 of the FD&C Act (21 U.S.C. 352)). Because the Agency considers contractors an "extension of the manufacturer's own facility," both Owners and Contracted Facilities are responsible for ensuring that their products are not adulterated or misbranded (21 CFR 200.10). As amended, the Act also specifies that current good manufacturing practice (CGMP) includes the implementation of quality oversight and controls over the manufacture of drugs, including the safety of raw materials, materials used in drug manufacturing, and finished drug products. See FDCA, as amended by the Food and Drug Administration Safety and Innovation Act (Pub.L. 112-144, Title VII, section 711). With respect to contract manufacturing, both Owners and Contracted Facilities must also work together to establish and maintain quality oversight of contracted manufacturing operations and the materials produced under contracted manufacturing arrangements.

B. Contract Manufacturing and Quality Management: Existing Guidance

Various Agency guidance documents indicate how quality management principles relate to contract manufacturing operations. These important guidance documents describe some of the roles and responsibilities of product Owners and Contracted Facilities.[6] The ICH guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (ICH Q7) recommends that manufacturers evaluate contractors for CGMP compliance both by establishing a formal agreement that delineates CGMP responsibilities, including quality measures, and also by auditing the contractor's facilities. Product Owners may hire another party "to perform the operational processes that are part of a manufacturer's inherent responsibilities" and "[Quality] systems call for quality agreements (contracts) that clearly describe the materials or service, quality specification responsibilities, and communication mechanisms."[7] The ICH guidance for industry *Q9 Quality Risk Management* (ICH Q9) recommends a comprehensive evaluation of suppliers and contract manufacturers through auditing and implementing supplier quality agreements.

Finally, the ICH guidance for industry *Q10 Pharmaceutical Quality Systems* (ICH Q10) states that the control and review of any outsourced activities is ultimately the responsibility of the "pharmaceutical company"—for the purposes of this guidance, the product *Owner*—, especially in ensuring that processes are in place to assure the control of activities outsourced to Contracted Facilities and the quality of purchased materials. ICH Q10 indicates that these processes should incorporate quality risk management and include the following critical activities:

[6] FDA's guidance for industry *Cooperative Manufacturing Arrangements for Licensed Biologics* provides additional information regarding the responsibilities of licensed biological product manufacturers and those of contract manufacturers.

[7] FDA's guidance for industry *Quality Systems Approach to Pharmaceutical CGMP Regulations* at 14.

- Before outsourcing manufacturing activities, the Owner should conduct a risk review that evaluates the extent of controls required for the particular supplier and the particular product or service covered by the agreement, and based on this risk, assess the oversight appropriate and assess the suitability and competence of the potential Contracted Facility(ies) to carry out the activity (e.g., audits, material evaluations, qualification).
- Owners and Contracted Facilities should define the responsibilities and communication processes for quality-related activities of the involved parties, and document these in a written agreement between the Owner and Contracted Facility.
- Owners should monitor and review the performance of the Contracted Facility and identify and implement any needed improvements.
- All parties performing manufacturing operations should monitor incoming ingredients and materials to ensure they are from approved sources using the agreed supply chain.[8]

These principles of quality management extend to contract manufacturing, and FDA expects parties engaged in contract manufacturing operations to implement quality management practices. This guidance is intended to build upon the quality management principles and recommendations outlined above and illustrate key points in developing and executing contracted manufacturing arrangements.

IV. DOCUMENTING CONTRACT MANUFACTURING ARRANGEMENTS IN QUALITY AGREEMENTS

When an Owner seeks the services of a Contracted Facility to perform all or part of the manufacturing, processing, packing, holding, or testing of a drug product, CGMP regulations (i.e., 21 CFR 200.10(b) and 21 CFR 211.22(a)) hold the Owner's Quality Unit ultimately responsible for approving and rejecting drug product manufactured by the contract manufacturer.[9] Further, under 21 CFR 210.2(b), the Contracted Facility must comply with CGMP regulations that apply to the operations in which that Contracted Facility is engaged. Although the CGMP regulations do not explicitly require Owners and Contracted Facilities to document their respective responsibilities in contract manufacturing arrangements, the regulations do require that Quality Unit responsibilities and procedures be in writing (21 CFR 211.22(d)). FDA believes that implementing a written Quality Agreement facilitates compliance with § 211.22(d). Therefore, FDA recommends that Owners and Contracted Facilities establish a written Quality Agreement to record their respective responsibilities in contract manufacturing arrangements. The following sections describe the Agency's current thinking regarding the documentation of agreed upon responsibilities 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 that defines and establishes the obligations and responsibilities of the Quality Units of each of the parties involved in the

[8] *See* FDA's guidance for industry *Q10 Pharmaceutical Quality System* (ICH Q10) at 7-8.

[9] Under 21 CFR 210.3(12), "manufacture, processing, packing, or holding of a drug product includes packaging and labeling operations, testing, and quality control of drug products." Accordingly, in this guidance, the operations performed by Contracted Facilities could also include those types of operations.

contract manufacturing of drugs subject to CGMP. In general, the Quality Agreement should clarify which of the CGMP activities are to be carried out by each party per the applicable regulations under 21 CFR parts 210, 211, 600-680, 1271, and other regulations that may apply. Quality Agreements are *not* commercial or business agreements; they do not cover issues such as general business terms and conditions, confidentiality, pricing or cost issues, delivery terms, or limits on liability or liquidated damages. FDA recommends that Quality Agreements be separate documents, or at least severable, from commercial contracts such as Master Services Agreements, Supply Agreements, etc., and that representatives from each party's Quality Unit and other relevant stakeholders participate actively in the drafting of Quality Agreements. While FDA does not routinely request or review business documents or business agreements on inspection FDA routinely requests and reviews evidence of Quality Agreements (or the lack of Quality Agreements).[10]

B. Elements of a Quality Agreement

A written Quality Agreement, describing the roles and responsibilities of the Owner and the Contracted Facility, should track the basic subparts of the CGMP regulations (or, for APIs, ICH Q7 guidance) to ensure coverage of all applicable CGMP responsibilities. A well-drafted Quality Agreement will use clear language to define key quality roles and responsibilities; establish communication expectations; provide key points of contact for both parties; specify what products and/or services the Contracted Facility will provide to or for the Owner; and establish who has final approval for various activities (Quality Units and other stakeholders). Most Quality Agreements contain the following basic sections:

- Purpose/Scope
- Terms (including effective date and termination clause)
- Dispute Resolution
- Responsibilities, including communication mechanisms & contacts
- Change control and revisions

The purpose and scope section will largely depend on the nature of contractual services being sought or provided under the agreement. Agreement on precise meaning of terms used in the Quality Agreement is an important step in drafting. Owners may consider adopting the terms and procedures used by Contracted Facilities in order to reduce the likelihood of misinterpretation and personnel error during actual manufacturing. The parties to a Quality Agreement should include a communication plan that explains how manufacturing deviations will be relayed to the Owner by the Contracted Facility, and how such deviations will be investigated, documented, and resolved. Dispute resolution provisions should also be included.

From a CGMP perspective, the most critical elements of a Quality Agreement are the sections delineating the parties' respective responsibilities and the discussion of change control. We take those topics up in turn here:

[10] See Compliance Policy Guide (CPG) Sec. 130.300, FDA Access to Results of Quality Assurance Program Audits and Inspections, and CPG Sec. 160.200, FDA Use of Income Tax Information from IRS in Compliance Activity.

1. Responsibilities

Owners and Contracted Facilities may opt to document the specific terms of their Quality Agreements with respect to CGMP responsibilities in a wide variety of formats, such as charts, matrices, or narratives, or a combination of these. Regardless of the format, however, each Quality Agreement should clearly document which party is responsible for CGMP activities relevant to the particular services or operations covered by the Quality Agreement. The Quality Agreement should cover any and all CGMP responsibilities relevant to the scope of the agreement. Depending on the scope of the services to be provided under the contract manufacturing arrangement, the Quality Agreement should indicate whether the Owner or Contracted Facility (or both) will handle specific activities related to each of the following topics:

a. Quality Unit responsibilities

The section that addresses Quality Unit responsibilities may be termed "Compliance," "Quality," "Quality Responsibilities," or any similar title. Whatever heading or category is selected by the parties, the section of the Quality Agreement covering Quality Unit responsibilities, perhaps the most critical element of a Quality Agreement, should define in detail the CGMP responsibilities of each party, including the quality activities and measures.

The assignment of particular responsibilities to either the Owner or Contracted Facility does not relieve any party from compliance with CGMP requirements that are not specifically set forth in the agreement. In particular, this section of the Quality Agreement should be clear with respect to product release. Owners are ultimately responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company. Although the Quality Unit of each Contracted Facility is responsible for release of the product of the operations it performs, final product release of finished goods for distribution must be carried out by the Owner and cannot be delegated to a Contracted Facility under the CGMP regulations or any terms of the Quality Agreement (21 CFR 211.22(a)).[11]

A Quality Agreement's discussion of Quality Unit responsibilities should further set out a communication plan regarding both verbal and written correspondence between the Owner and Contracted Facility, including information on appropriate personnel to contact at each party. Additionally, FDA expects that Quality Agreements will specify that services provided by Contracted Facilities (including laboratories) will comply with CGMPs and any applicable local (state and national) authorities as agreed by the parties.

Quality Agreements should also provide for Owners to evaluate and audit Contracted Facilities to ensure CGMP compliance for the specific operations occurring at the contract sites; this

[11] See Preamble to Title 21, Subchapter C, Human and Veterinary Drugs, Current Good Manufacturing Practice in Manufacture, Processing, Packing, or Holding, Paragraph 97, discussing 21 CFR 211.22(a): "This paragraph clearly says that the quality control unit of a contracting firm must approve or reject drug products produced by contractors. The Commissioner believes this is proper because, in the circumstances described, the contractor does not own the goods, but merely performs a service for the contracting firm. *The responsibility to approve release of a drug product for distribution must rest with the owner of the drug product*." (43 FR 45014 at 45034 (29 September 1978) (emphasis added)).

provision should cover both routine quality audits conducted on a regular basis as well as for-cause audits. Depending on the nature of the product(s) to be manufactured and services to be provided, Quality Agreements should account for the parties' expectations with respect to regulatory inspections (e.g., pre-approval inspections, routine surveillance, or for-cause); the parties' respective obligations on reporting inspectional observations and findings, as well as Agency actions, should be described in the Quality Agreement. Because Contracted Facilities often simultaneously or sequentially provide services to multiple product Owners, special consideration should be given to reporting information about objectionable conditions observed during inspections and audits of the Contracted Facility, regardless of which products were covered on inspection. The Quality Agreement should also indicate how the parties will communicate information about preventing cross-contamination and maintaining traceability when a Contracted Facility processes or tests drugs for multiple product Owners.

b. Facilities and equipment

This section of a Quality Agreement should identify the specific site(s) at which manufacturing operations will be performed along with addresses and the particular services to be provided at each. The parties should indicate which party will be responsible for carrying out validation, qualification, and maintenance activities for any relevant equipment or equipment systems, such as 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.

c. Materials management

In this section, the parties should indicate who is responsible for setting specifications for raw materials; auditing, qualifying, and monitoring suppliers of those materials; and conducting required sampling and testing. The Quality Agreement should also address how the parties are to ensure appropriate inventory management, including procedures for labeling, label printing, and reconciliation, as well as procedures for quarantine and prevention of mix-ups and cross-contamination. Additionally, the Quality Agreement should allocate responsibilities between the parties for storing materials under labeled conditions, including maintenance of required storage conditions until material transfer from one party to the next (whether from Contracted Facility back to the Owner or to another Contracted Facility for further operations).

d. Product-specific terms

A comprehensive Quality Agreement will provide specific terms related to the particular product or products involved. The Owner and Contracted Facility might opt to include this information in an appendix, or directly in the body of the Quality Agreement. Regardless, this section of the Quality Agreement should include 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; and provisions for the presence of Owner personnel ("person in the plant") in the Contracted Facility as agreed upon by the parties.

The Quality Agreement should also indicate how Owners of both application and non-application drug products will transfer knowledge—e.g., product/process development information -- to their Contracted Facilities to assure a quality product can be produced in compliance with CGMP. Owners of application products should evaluate any application commitments that bear upon CGMP activities and consider sharing relevant information necessary for the Contracted Facility to comply with CGMP and the Act.

e. Laboratory controls

The Quality Unit of each participating party to a Quality Agreement should have adequate laboratory facilities available to them for testing and approval (or rejection) of drug products (see 21 CFR 211.22(b)). Quality laboratory operations performed by any party in relation to a finished pharmaceutical should be performed in accordance to with CGMP at each site with which the applicable laboratory operations occur. Procedures delineating controls over sampling and testing samples should be established in the Quality Agreement. Both the Owner and Contract Laboratory should be responsible for ensuring that the methods used are validated and have been transferred appropriately (if the development, qualification, and validation have not been done on site). Laboratory equipment used to perform CGMP operations should be qualified, calibrated, and maintained in a controlled state with the primary responsibility resting on the Contract Laboratory; however, the Owner should ensure that the Contract Laboratory is functioning in accordance to with CGMP through routine auditing. If the Owner uses Contracted Facilities for the storage and routine testing for stability and reserve samples, the Quality Agreement should delineate the frequency of testing and timely communication of the results. The parties should also indicate who will be responsible for investigating deviations, discrepancies, failures, and out-of-specification results in the laboratory.

f. Documentation

Nothing about a Quality Agreement between the product Owner and Contracted Facilities exempts any participating party from maintaining documentation and records required under the CGMP regulations. The Quality Agreement should indicate procedures for the Owner to review and approve documents and any changes thereto, such as Standard Operating Procedures, manufacturing records, specifications, laboratory records, validation documentation, investigation records, annual reports, and any other documents/records related to the product manufactured or services provided by the Contracted Facility. The parties should also specify how records and documentation required by the applicable CGMP regulations will be made available for immediate retrieval, and how copies will be made and maintained under a certification or controlled copy procedure (21 CFR 211.180). If either party utilizes electronic recordkeeping systems, the Quality Agreement should indicate that any electronic records will be stored in such a manner as to maintain their traceability, reliability, and integrity throughout the required record keeping timeframes established in applicable regulations.

2. Change Control, Including Subcontractors

Changes may be initiated by either party for many reasons and should be discussed and addressed in the Quality Agreement.

The Contracted Facility should notify the Owner of changes, including but not limited to, raw materials and starting materials and their suppliers; establishment locations; manufacturing processes; additional products brought into the line, train, or facility: testing procedures: major manufacturing equipment: shipping methods; lot numbering scheme: container closure systems; tamper evidence features: key personnel; and product discontinuation. Owners and Contracted Facilities should both be aware that the following may initiate changes and should therefore be communicated to other parties in the contract manufacturing arrangement: investigations into manufacturing deviations and out-of-specification results, new or revised product claims, stability studies, process capability analysis and trending, process improvement projects, field alert reports/biological product deviation reports, customer complaints, recalls, or adverse event reports.

The Owner and Contracted Facility should agree upon and document in the Quality Agreement the types of changes for which Owner review and approval must be obtained before implementation and those changes that can be implemented with notification only. Some changes may be deemed to present lower risk to product quality and may not necessitate notification at all, but those should be carefully considered by the Owner and clearly set forth in the Quality Agreement. The parties should also discuss, agree upon, and document procedures for conducting validation activities required to implement any changes.

V. ILLUSTRATIVE SCENARIOS

The following hypothetical scenarios illustrate some common problems in contracted manufacturing arrangements and depict ways in which both Owners and Contracted Facilities can impact product quality. The scenarios also demonstrate our thinking regarding possible resolution of the problems. The examples provided are not intended to be exclusive, but, instead, to provide industry and other stakeholders with some frequently-encountered fact patterns and our analysis of those facts.

A. A Quality Agreement Does Not Exempt Contracted Facilities From CGMP Requirements Related to the Operations they Perform, Regardless of Whether Such CGMP Requirements are Specifically Discussed in the Quality Agreement

1. Case 1: Responsibility for Facilities and Equipment Maintenance and Upkeep at Contracted Facility

FDA inspection of a Contracted Facility that manufactures injectable product for the product Owner reveals significant objectionable conditions at the Contracted Facility. A Warning Letter is issued to the Contracted Facility; most of the conditions observed are related to deficient maintenance of the facilities and equipment used to manufacture the injectable product, such as defective or partially broken equipment, visibly tarnished piping, leaking seals, etc. In addition, facility design is inadequate to prevent contamination. This Contracted Facility has a Quality Agreement specifying the product Owner's responsibility for upgrades and maintenance of the facilities and equipment. The Owner fails to provide the requisite resources or carry out the necessary upgrades and maintenance, but and the

Contracted Facility continues to manufacture the product under non-CGMP conditions that could result in product contamination.

2. Case 2: Responsibility for Documenting Steps in the Manufacturing Process

The Contracted Facility is responsible for contract manufacturing of a prescription product subject to the product Owner's ANDA. On inspection, it is observed that the Contracted Facility's batch records do not accurately reflect the actual manufacturing process because the batch records do not document the addition of reclaimed powder. The Contracted Facility claims that this practice of incomplete batch records was in accordance with the wishes of the product Owner.

A Quality Agreement does not exempt Contracted Facilities from CGMP requirements related to the operations they perform, regardless of whether the Quality Agreement specifically discusses those CGMP requirements. In either of the two cases described above, the Contracted Facility could be responsible for CGMP failures, because, regardless of the allocation of responsibilities in the Quality Agreement, the Contracted Facility cannot essentially agree to manufacture under non-CGMP conditions. The Quality Agreement is not a substitute for compliance with CGMP requirements by either party. The lesson from cases like these is that Contracted Facilities should insist on greater clarity regarding how Owners will carry out specific obligations under the Quality Agreement, because the Quality Agreement will not serve as an excuse for manufacturing drugs in a non-compliant environment. When the terms of the Quality Agreement prove inadequate during the lifetime of the contractual relationship, the Contracted Facility could refuse to continue to manufacture the product under non-CGMP conditions (e.g., in Case 2, the Contracted Facility could refuse to carry out the additional manufacturing step without including it in the batch record). Another option would be for the Contracted Facility to bear the costs for modifying operations in order to maintain CGMP compliance, and then seek redress from the Owner later (in Case 1, for example, the Contracted Facility might purchase necessary equipment, carry out cleaning, upgrades, validation, and repairs, etc., and then charge the costs to the Owner). In any case, stipulations in the Quality Agreement do not relieve the Contracted Facility of its obligations to meet CGMPs relevant to the operations it performs.

At the same time, the Owner is not relieved of its responsibility to ensure the quality and safety of the products it introduces or causes to be introduced to the marketplace because a Quality Agreement allocates a particular activity to the Contracted Facility. For example, after finding the types of problems at Contracted Facilities in the two cases above, FDA could inspect the Owner. Depending on the evidence gathered, FDA could also hold the Owner liable responsible for CGMP failures, or for oversight failures in monitoring the activities of the Contracted Facility in order to ensure that its products are manufactured under CGMP conditions. Depending on the significance, such failures on the part of a product Owner could be grounds for a product recall, or for a seizure, injunction, or other action. Additionally, for foreign sites, the Agency could consider refusing the Owner's products entry into the United States.

B. Contract Laboratories are Contracted Facilities Subject to CGMP Requirements

1. Case 3: Responsibility for Data Integrity in Laboratory Records and Test Results

> In this scenario, a Contracted Facility providing contract analytical laboratory services repeatedly reports passing results in its CGMP records when failures were obtained in actual analysis. The Contracted Facility also fails to report accurate results to its client, the product Owner. When FDA inspects the Owner, it is revealed that the Owner did not audit the contract laboratory prior to FDA's inspection of the Owner, despite the fact that the Owner has a written procedure in place requiring a site audit of contracted facilities every two years.

2. Case 4: Responsibilities for Method Validation

> Routine inspection of this Contract Laboratory discloses its failure to conduct complete investigations of out-of-specification results and sample duplication failures reported for stability samples of an injectable product, and for the failure to implement adequate corrective actions. Some of the investigations suggest that sample duplication failures were related to analytical techniques in sample preparation, but the specific problematic techniques are not clearly identified in the investigations and in the analytical method. The Contract Laboratory's management claims that, since the method they used for testing belonged to the NDA holder, the Contract Facility is not responsible for investigating and implementing corrections related to the analytical method. Despite the Contracted Facility's knowledge that the method is not suitable, and is therefore not compliant with CGMP, the laboratory continues to use the questionable method to test the product.

Contract Laboratories are Contracted Facilities like any others, and they are responsible for complying with CGMPs that relate to the operations they perform, regardless of the specific terms of any Quality Agreement they have reached with the product Owner. As a part of those responsibilities, they must employ controls to assure the integrity and reliability of the data they generate, and, in addition, they must provide data and test results that the Owner can use in final disposition decisions. In either of the cases above, the Contracted Facilities could be held responsible for clear CGMP violations related to the laboratory activities they conduct. Additionally, the Owners could be responsible for CGMP violations because, regardless of who tests the products or the agreements in place regarding the manufacturing and testing of those products, the Owner is ultimately required to ensure that the products are manufactured in accordance with the Act, assuring the identity, strength, quality, purity, and safety of the products. The Owners might further be cited for failure to follow their own procedures for evaluating, qualifying, auditing, and monitoring contractors/suppliers.

V. CONCLUSION

Written Quality Agreements are not explicitly required under existing CGMP regulations and do not relieve either party of their responsibilities under CGMP regulationss or under the Act. However, Owners and Contracted Facilities can draw on quality management principles to carry out the complicated process of contract drug manufacturing by defining, establishing, and

documenting the responsibilities of all parties involved in drug manufacturing, testing, or other support operations. Accordingly, FDA recommends that Owners and Contracted Facilities implement written Quality Agreements as a tool to delineate responsibilities and assure the quality, safety, and effectiveness of drug products.