



AFDO 118th Annual Educational Conference Contract Manufacturing Arrangements for Drugs: Quality Agreements **

**Plus Exciting Bonus Info On CGMP Policy Development!!

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Objectives

- Brief background
 - Where do guidance documents fit into the regulatory scheme?
 - What are the types of guidance documents?
- CGMP Guidances
 - Practical matters
 - Recent GFIs & GFIs of Interest—Details on Contract Manufacturing/Quality Agreements
- References and Help!

Admin Law 101

- Congress says what is mandatory in the Act (FDCA or PHSA, etc.)
- Secretary (delegated to FDA) promulgates regulations that indicate details about what is required by the Act (21 CFR 210 & 211, 600s, etc.)
- Guidance documents describe FDA's current thinking on a particular topic
 - Not binding on FDA or any party*

Types of Guidances

- GGPs (21 CFR 10.115) establish 2 types
- Level 1:
 - First interpretations of statutory or regulatory requirements
 - Changes in interpretation or policy (not minor in nature)
 - Complex scientific and highly controversial issues
 - May solicit public input before issuance, but comments can be submitted at any time
- Level 2:
 - Existing practices or minor changes in interpretation or policy
 - Level 2 guidances post directly to the internet

Documents that are not “Guidance for Industry” (but we know you look at them)

- Compliance Policy Guides (CPGs)
 - advise field inspection and compliance staff on standards and procedures for determining industry compliance
 - <http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/default.htm>

- Compliance Program Guidance Manuals (CPGMs)
 - instructions to FDA staff for obtaining information to help fulfill agency plans in the specified program areas
 - <http://www.fda.gov/ICECI/ComplianceManuals/ComplianceProgramManual/default.htm>

Some Practical Matters

- All Human Drug GFIs on the web at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>
 - For CGMP GFIs, click “Current Good Manufacturing Practices (CGMPs)/Compliance”
 - Don’t forget about International Conference on Harmonisation (ICH)-- especially the “Q”s (more later)

- Guidance Agenda:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM314767.pdf>

- New/Revised/Withdrawn List:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM254636.pdf>

- Comments:
 - You can comment on any guidance at any time.
 - Especially for drafts, submit electronically at www.regulations.gov

Recent CGMP Guidances*

- Contract Manufacturing Arrangements for Drugs: Quality Agreements (Draft 05/24/13)

- Level 2 CGMP Q&A
 - Process Controls/Powder Blends and Stratified Sampling (08/06/13)
 - Process Controls/PAT (09/16/13)

*Excludes PET drug guidance documents and ICH documents

Contract Manufacturing Arrangements for Drugs: Quality Agreements

- Draft Guidance published May 24, 2013
- Comment period closed July 29, 2013
- Purpose: describe how Quality Agreements can be used to define, establish, and document the responsibilities of the parties involved in contract manufacturing of drugs

First Stop: Statute

- **501(a)(2)(B)**: A drug is ***adulterated*** if...
 - methods used in, or facilities or controls used for, manufacturing, processing, packing, or holding do not conform with **CGMP**

- FDASIA § 711: “**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.”
 - Explicitly links CGMP to quality management activities

Statutes Beget Regs...

The **CGMP** regulations don't explicitly require a **written Quality Agreement**, but...

- 21 CFR 200.10: **Contract manufacturers** are an extension of the manufacturer's own facility
- 21 CFR 210.1: Failure to comply with **CGMPs** render the drug **adulterated** and subject to regulatory action
- 21 CFR 210.2(b): if only some operations, must comply with **CGMPs** applicable to those operations
- 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
- 21 CFR 211.22(a): **Quality** unit is responsible for approving or rejecting drug products manufactured, processed, packed, or held under **contract** by another company
- 21 CFR 211.22(d): **Quality** unit procedures & responsibilities must be in **writing**

Draft Guidance on Quality Agreements: Scope

- What is covered:
 - human drugs, veterinary drugs, biological and biotechnology products, finished products, active pharmaceutical ingredients (APIs or drug substances, or their intermediates), and drug constituents of combination drug/device products
 - “manufacturing” includes processing, packing, holding, labeling operations, testing, and operations of quality unit

- What is *not*:
 - Type A medicated articles and medicated feed, medical devices, dietary supplements, or HCT/Ps
 - qualification activities, auditing, or disqualification of contracted facilities
 - controls related to qualification, auditing, monitoring, or disqualification of suppliers of raw materials or ingredients, including recommendations for Quality Agreements with vendors/suppliers
 - distributors

Draft Guidance on Quality Agreements: Goals

- Outlines critical roles played by both Owners and Contract Facilities
- Explains how manufacturers should use Quality Agreements to define, establish, and document their responsibilities
- Emphasizes that Quality Agreements should:
 - define parties' responsibilities
 - assure full CGMP conformance, and
 - facilitate consistent delivery of safe and effective medicines

Draft Guidance on Quality Agreements: Definitions

- **“Owner”** and **“Contract Facility”** are deliberate choices
 - Why not “Contract Giver” and “Contract Acceptor?”

- **Quality Agreement**
 - comprehensive written agreement
 - defines and establishes obligations and responsibilities of Quality Units of parties involved in contract manufacturing of drugs subject to CGMP
 - Versus “Supply Agreement” or “Technical Agreement” or other possibilities

Draft Guidance on Quality Agreements: Key Elements

- Clear language to define key quality roles and responsibilities
- Communication expectations & POCs
- Products and/or services
- Approval for various activities (Quality Units and other stakeholders)
- Basic Sections:
 - Purpose/Scope
 - Terms (including effective date and renewal/extension)
 - “Dispute Resolution”—how will disagreements be elevated to decision-makers in each company (*not* ADR or arbitration, etc.)
 - Responsibilities, including communication mechanisms & contacts
 - Change control and revisions

Draft Guidance on Quality Agreements: Responsibilities

- ***Owners***
 - Final approval or rejection of drug product to the market (211.22(a))
 - Cannot be delegated to Contract Facility or via a Quality Agreement

- ***Contracted facilities***
 - CGMPs for all operations performed, including promptly evaluating and addressing manufacturing or quality problems
 - Quality Unit product disposition (e.g., release, reject) decision for each operation it performs

- ***Everyone***
 - Compliance with all CGMPs
 - Product quality
 - Patient safety

Draft Guidance on Quality Agreements: Change Control

- Document changes that can be implemented by the Contract Facility
 - Without any notice to the Owner
 - With notification, but not prior approval by Owner
 - Only after Owner reviews and approves

- What risks might the type of change contemplated present to product quality?

- Discuss, agree upon, and document procedures for conducting validation activities required to implement any changes

FDA Inspections and Quality Agreements

- No *new* rules at play—continue to inspect against the FDCA & CGMP regulations, and all parties continue to be subject to the same requirements
- FDA routinely requests and reviews evidence of Quality Agreements (or the lack of Quality Agreements)
 - Implication: tough to engage in compliant contract drug manufacturing without a written Quality Agreement
 - The absence of a written Quality Agreement is not a 483 deficiency.

Warning Letters

- Could a well-written, well-thought-out Quality Agreement have prevented or helped reduce the likelihood of these situations?
- Can firms use Quality Agreements to demonstrate intent to follow CGMPs?

WL to Contract Facility

- “...you state that you have informed your clients on the importance of validating the methods, but they have chosen not to validate the methods. In addition, you state that you will inform them again in writing.”
- “Your response, however, is inadequate because you do not provide your firm's planned corrective actions for this CGMP violation. ***You are responsible for ensuring that the test methods used by your firm are validated.***”
- “Data...generated by an unvalidated method(s)...should not be used for establishment of expiration dates, commercial batch release, or other CGMP decisions.”

WL to Contract Facility

- “Your firm does not have adequate written procedures for production and process controls...[under 211.100(a)]...You conducted validation activities for only products X and Y, which you deemed to be the “worst case” products...you have not provided a scientific rationale to demonstrate that the mixing studies for X and Y are adequate and fully representative...for the other 118 products...Unless you are able to demonstrate that your matrix approach is scientifically sound, all products must be individually validated.”
 - *Copies of WL to CEOs of five of Contracted Facility’s customers.*

WL to Owner

- “Your firm is the owner of this drug product, but did not adequately evaluate whether the CMO..., which is an extension of your operations, can consistently produce product that is suitable for distribution. For example, ***your quality unit did not evaluate the quality of each batch of drug product produced by the CMO in order to make an appropriate disposition decision*** (approval or rejection).”
- “Your finished product, XXXX, was not tested for conformance to the labeled amount of active ingredients. Your firm contracted out the XXXX product. ***Your firm accepted and relied on the Certificate of Analysis (COA) from your contract manufacturer (CMO) and failed to verify the accuracy and completeness of testing results in the COA.*** For example, XXXX contains six active ingredients. The COA for this lot showed that only identity testing for two of the six active ingredients was conducted. No assay testing was conducted.”

WL to Owner

- “...we are concerned about your firm’s fundamental understanding of what is required by your QCU and the regulatory expectations for a firm that enters into agreements with contract manufacturers to manufacture drug products. Although you have agreements with other firms that may delineate specific responsibilities to each party (e.g., quality control responsibilities), ***you are ultimately responsible for the quality of your products.***
- ***Regardless of who manufactures your products or the agreements in place, you are required to ensure that these products meet predefined specifications prior to distribution and are manufactured in accordance with the Act and its implementing Regulations.”***

WL to Owner

- “...We are also concerned about your firm’s fundamental understanding of the overall regulatory expectations for a firm that enters into agreements with contract testing laboratories, including the critical quality unit responsibilities required by 21 CFR 211. ***Although you have agreements with other firms that may delineate specific responsibilities to each party..., you are ultimately responsible for the quality of your products.*** The Food and Drug Administration is aware that many manufacturers of pharmaceutical products utilize extramural independent contract facilities...and regards extramural facilities as an extension of the manufacturer's own facility. ***Regardless of who performs your operations, or the agreements in place, you are required to ensure your products were made in accordance with section 501(a)(2)(B) of the Act so as to provide for their identity, strength, quality, purity, and safety, and are suitable for marketing.***”

WL to Both: “Two-fer”

Contract Facility (contract test lab) repeatedly reported passing results when failures were obtained; also failed to report accurate results to client.

- Contract Facility: “As a contract laboratory that tests drugs, your firm is responsible for complying with CGMP. In addition, it is also essential that your firm provide test results for evaluation and consideration by the owner of the product to consider in its final disposition decision.”
- Owner: Failure to properly evaluate contract laboratory to ensure CGMP compliance of operations occurring at the contract site. Did not audit the CTL; after FDA inspected, Owner audited and found critical and major deficiencies.
 - “Although you have agreements with other firms that may delineate specific responsibilities for each party, you are ultimately responsible for the quality of your products and the reliability of test results. Regardless of who tests your products or the agreements in place, you are required to manufacture these products in accordance with the Act to assure their identity, strength, quality, purity, and safety.”

Draft Guidance on Quality Agreements: Summary

- Owners and Contract Facilities should work together proactively to characterize and control risks to product quality and patient safety
- Everyone is responsible for Quality
- A well-drafted Quality Agreement will:
 - Promote communication between the parties
 - Clearly delineate the parties' responsibilities, especially with respect to quality issues
 - Assure coverage of all CGMP requirements
 - Provide for change management
- Practical, positive consequences for patients and your business

Recent CGMP Guidances*

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Level 2 CGMP Q&A*

- Questions and Answers on Current Good Manufacturing Practices (CGMP) for Drugs
 - Level 2 Guidances
 - Most recent updates: Process Controls (PAT and Powder Blends/Stratified Sampling; August & September 2013)
 - <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm124740.htm>
- Pyrogen and Endotoxins Testing: Questions and Answers (06/28/12)
- Dosage Delivery Devices for Orally Ingested OTC Liquid Drug Products (5/4/2011)
- Process Validation: General Principles and Practice (01/24/11)
- Use of Mechanical Calibration of Dissolution Apparatus 1 and 2 (01/26/10)
- Pharmaceutical Components at Risk for Melamine Contamination (08/06/09)
- Current Good Manufacturing Practice for Phase 1 Investigational Drugs (07/14/08)

*Excludes PET drug guidance documents and ICH documents

Other Important GFIs*

- Testing of Glycerin for Diethylene Glycol (05/01/07)
- Investigating Out-of-Specification Test Results for Pharmaceutical Production (10/11/06)
- Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations (09/27/06)
- PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance (09/29/04)
- Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice (09/29/04)
- ICH Q7, Good Manufacturing Practice for Active Pharmaceutical Ingredients (08/01/01)

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Some Extras

- All you ever wanted to know about FDASIA
<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAAct/SignificantAmendmentstotheFDCAAct/FDASIA/default.htm>
 - FDASIA-Track <http://www.fda.gov/AboutFDA/Transparency/track/ucm328907.htm>
- Semi-Annual Agenda (HHS; Jan '14)
<http://www.gpo.gov/fdsys/pkg/FR-2014-01-07/pdf/2013-29632.pdf>
- Drug Shortages
<http://www.fda.gov/downloads/Drugs/DrugSafety/DrugShortages/UCM372566.pdf>
 - Drug Shortages Strategic Plan (Oct '13)
<http://www.fda.gov/drugs/drugsafety/drugshortages/default.htm>
- Compounding
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/default.htm>

You've Got Questions? We've Got Answers!

- **CGMP Subject Matter Contact List**

<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm096102.htm>

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