FDA's Current Thinking on Quality Agreements and Contract Manufacturing

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What we'll cover

- Final Guidance on Contract Manufacturing Arrangements for Drugs: Quality Agreements
  - Definitions and Elements
  - Highlights and Expectations
- Application
  - Recent WL
  - Considerations & Perspectives

Legal Framework: FD&C Act

- 501(a)(2)(B): A drug is *adulterated* if:

  the 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.

  - CGMP linked to quality management activities

Legal Framework: Relevant Regs (I)

- 21 CFR 210.1: Failure to comply with CGMP renders the drug adulterated and subject to regulatory action.
- 21 CFR 210.2(b): If you only contract for some operations, those operations must comply with applicable CGMP.
  - **You can't "contract around" CGMP!**
- 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.

Legal Framework: Relevant Regs (II)

- CGMP regs don't explicitly require a written quality agreement, but…
- 21 CFR 211.22(a): QU is responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company.
- 21 CFR 211.22(d): QU procedures and responsibilities must be in writing.
- 21 CFR 200.10: Contract manufacturers are an extension of the manufacturer's own facility.

Everything New is Old: Previous FDA Guidance

- **FDA GFI, Quality Systems Approach to Pharmaceutical CGMP (2006):**

"Outsourcing involves hiring a second party under a contract to perform the operational processes that are part of a manufacturer's inherent responsibilities…Quality systems call for contracts (quality agreements) that clearly describe…"

  - Materials, services
  - Specification-setting responsibilities
  - Communication
  - Training, qualifications, monitoring
  - Harmony with the parties' quality standards

Everything New is Old: Previous FDA Guidance

- FDA GFI, Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production (2006)

"This guidance can also be used by contract firms performing production and/or laboratory testing responsibilities…"

  - Responsibilities of manufacturing firms and CTLs for compliance with CGMP requirements are "the same."
  - Emphasizes importance of conveying data, findings, and supporting documentation to the manufacturing firm's QU for full-scale OOS investigation.
  - "It is…critical for the laboratory to provide all test results for evaluation and consideration by the [QU] *in its final disposition decision*. In addition, when investigation by a contract laboratory does not determine an assignable cause, all test results should be reported to the customer on the certificate of analysis.

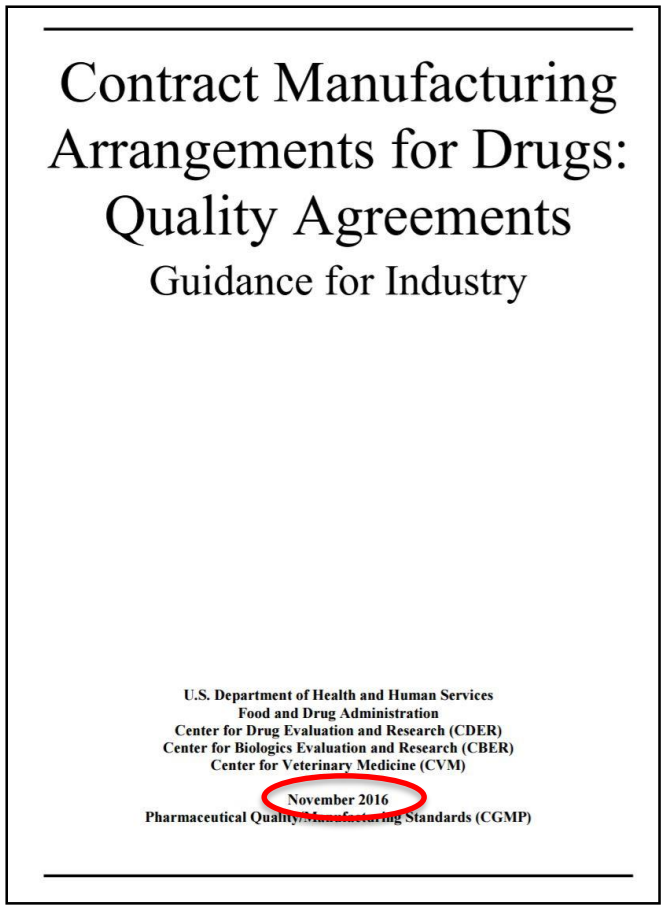
ICH

- **ICH Q10**: “The pharmaceutical company is ultimately responsible to ensure processes are in place to assure the control of outsourced activities and quality of purchased materials. These processes should incorporate quality risk management.”
- **ICH Q9**: “Comprehensive evaluation of suppliers and contract manufacturers, for example, by auditing and implementing supplier quality agreements.”
  - Sponsor’s quality system drives management of outsourced activities.
  - Members in the supply chain are partners in determining success.
- **ICH Q7 (API)**
  - CMOs (including labs): comply with CGMP in Q7
  - Manufacturers: evaluate CMOs to ensure CGMP compliance for contracted operations
  - Written agreement

Expectations and Recommendations

- QA as part of a larger outsourcing risk management plan
- Tools:
  - Risk Management Strategy
  - Process Maps
  - Supplier Quality Questionnaire
  - Communications Infrastructure
  - Audit Program
  - Quality Agreements
  - Metrics/Analytics Program
  - Report cards

Now Final: FDA Guidance on Quality Agreements



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)

Quality agreements can be used to define expectations and responsibilities in a contract manufacturing arrangement up front.

Scope of Guidance

What is covered:

- human drugs
- veterinary drugs
- biological and biotechnology products
- finished products
- active pharmaceutical ingredients (API or drug substances or their intermediates)
- 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
- 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

Purpose

- Outlines critical roles played by both product owners and contracted 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

Definitions

- ***Manufacturer***: an entity that engages in CGMP activities, including implementation of oversight and controls over the manufacture of drugs to ensure quality.
- ***Owners***: manufacturers of APIs, drug substances, in-process materials, finished drug products, including biological products, and certain 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.
- ***Contract Facilities***: parties that perform one or more manufacturing operations on behalf of an owner or owners.
- ***Quality Agreement***: 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.

Take-home: Elements

- Clear language to define key quality roles and responsibilities
- Communication expectations and POCs
- Products and/or services
- Approval for various activities (Quality Units and other stakeholders)
- Basic Sections:
  - Purpose/Scope
  - Definitions of terms specific to the agreement
  - Resolution of disagreements — how will you resolve disagreements about product quality issues or other problems?
  - Manufacturing activities —quality unit and other activities associated with manufacturing processes & control of changes to manufacturing processes
  - Life cycle/revisions to the agreement

Take-home: Responsibilities

- ***Owners***
  - Final approval or rejection of drug product to the market (211.22(a))
  - Cannot be delegated* to Contracted Facility or via a Quality Agreement
- ***Contract facilities***
  - CGMP 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 CGMP
  - Product quality
  - Patient safety

Take-home: Change-Control

- Document changes that can be implemented by the contracted 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.