# *Putting the 'Quality' in Quality Agreements for Contract Manufacturing Operations*

Paula Katz

**Manufacturing Quality and Guidance Policy Staff Director**
**Office of Manufacturing Quality**
**CDER Office of Compliance**

Nov. 3, 2016
Parenteral Drug Association
Outsourcing/CMO Conference
Washington, DC

# *What we'll cover*

- Background
  - Why Outsource?
  - Legal Framework
- Draft Guidance on *Quality Agreements in Contract Manufacturing*
  - Scope and purpose
  - Definitions
  - Highlights and Expectations
- Enforcement Perspectives and Outcomes

# Context

- Contract manufacturing as a subset of "outsourcing"
- Manufacturing services vs. purchase of goods, raw materials, components (upstream); distribution services (downstream of finished goods)
- Similar concepts and principles

# *Why outsource? Owners want…*

- Faster, better, stronger
- Niche expertise
- Increased capacity
- Resource shifting
- Shorter time to market
- Temporary solution


# *Outsourcing: Contracted facilities provide…*

- Unit Ops: micronizing, sterilizing, etc.
- Analytical testing, control labs
- Packaging, labeling
- Others



# 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.**

  ✓This explicitly links CGMP 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)

- The 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.

# *Previous FDA Guidance: Quality Agreements*

- 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

# *ICH & Quality Risk Management*

- **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.

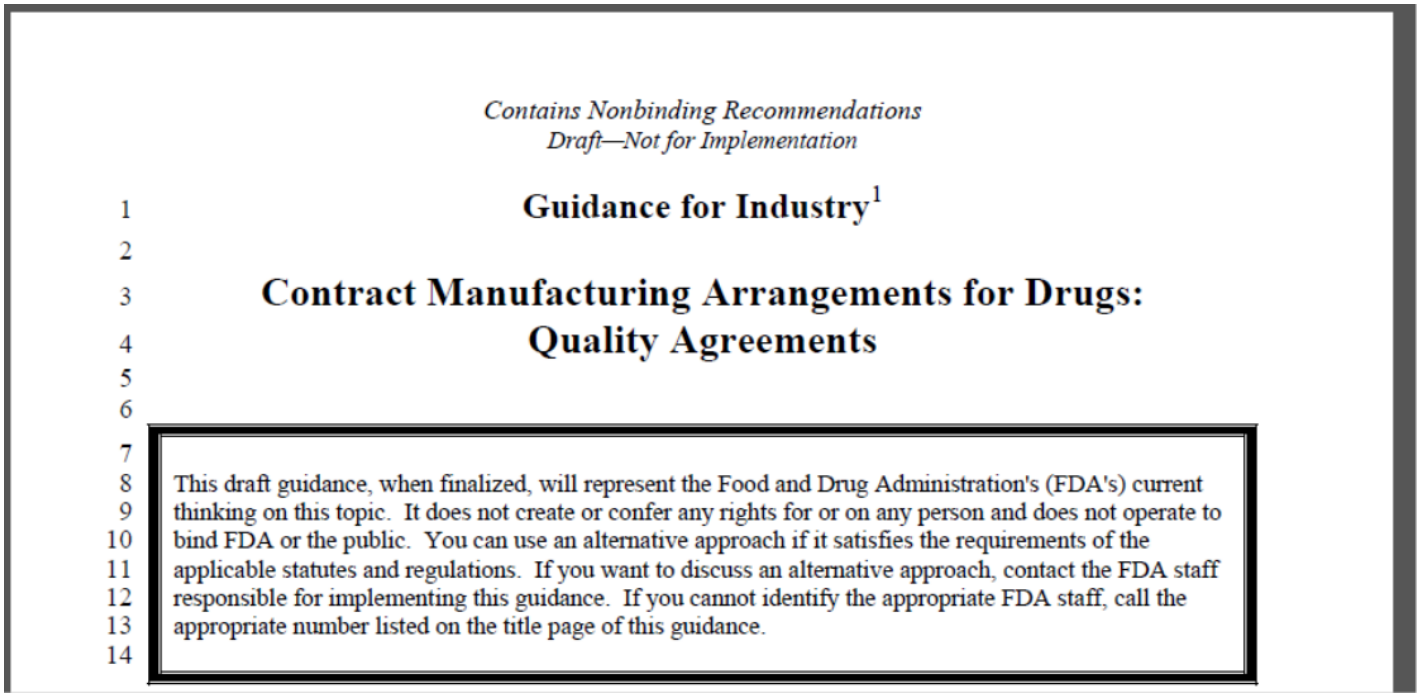
- **ICH Q7 (API)**
  - CMOs (including labs): comply with CGMP in Q7
  - Manufacturers: evaluate CMOs to ensure CGMP compliance for contracted operations
  - Written agreement

# *Expectations and Recommendations*

- QA as part of a larger outsourcing risk management plan
  - Say what you do, do what you say, prove it, improve it
  - Deming
- Tools:
  - Risk Management Strategy
  - Process Maps
  - Supplier Quality Questionnaire
  - Communications Infrastructure
  - Audit Program
  - Quality Agreements
  - Metrics/Analytics Program
  - Report cards

# *Draft Guidance—May 2013*

- http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM353925.pdf



*Contains Nonbinding Recommendations*
*Draft—Not for Implementation*

**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.

# *Scope of Draft 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

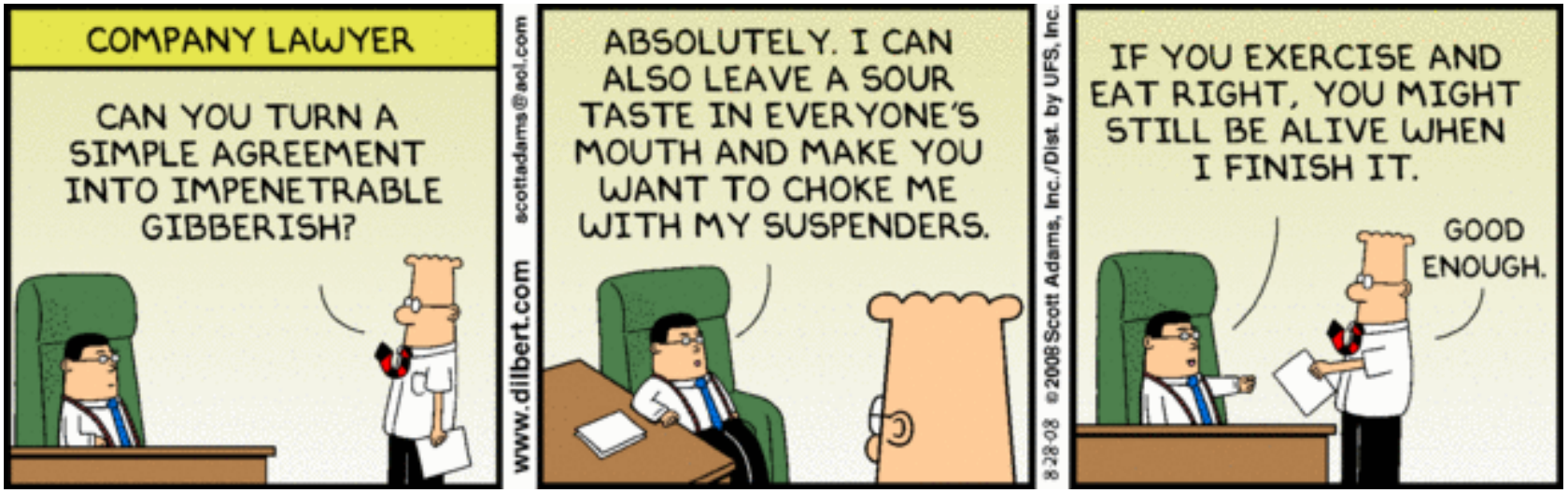
# *Purpose*

- 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

# *Language and Definitions*

- "Owner" and "Contracted 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

# *Food for thought…*



# *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
  - 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

# *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
- ***Contracted 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.

# *What to Expect When We're Inspecting*

- No *new* rules at play—continue to inspect against the FD&C Act and 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: Compliant contract drug manufacturing without a written Quality Agreement is difficult.

# *Enforcement Perspectives: Outcomes*

- Warning/Untitled Letters
- Regulatory Meetings
- Seizures, Injunctions
- PAI Withholds
- Recalls
- Reputational Harms—Patients, Industry

# *WL to Contracted Facilities: Pointing Fingers*

- "…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 Contracted Facilities: Communication*

- "…you failed to address the impact of the observed method deficiencies on the test results provided to your customers and to indicate whether you will ***inform your customers*** of the result of such evaluation."

- "Your response, however, is inadequate because it does not include an evaluation of the data already provided to your clients, which were generated using the unqualified reference standards and unstandardized titrant solutions. Furthermore, your response does not indicate ***whether you will inform your customers of the result*** of such evaluation as it relates to their drug product(s)."

# *WL to Contracted Facilities: Data Integrity*

- "…Please note that as a contract testing laboratory, it is your responsibility to ensure the integrity of the data generated and that all test results be properly documented, maintained, and reported."
- Failure to investigate OOS: "Please indicate if all your customers were notified of these failures and date of notification."

# *WL to Contracted Facility: CC Your Customers!*

- "You released finished drug products…to your customer without conducting or reviewing release testing to determine if your products conformed to their specifications…FDA laboratory analysis indicated that the drug was sub-potent for both labelled active ingredients…Your written quality agreement with XXXX indicates that XXXX is responsible for final product release to the market. The same agreement also states that [you are] responsible for release of products to the customer, but you did not conduct any laboratory analysis to determine whether your products conformed with specifications prior to releasing them to [your customer]."
- Based on FDA's analysis, Customer recalled all lots in expiry.

# *WL to Contracted Facility: CC Your Customers! (cont.)*

- "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 Product Owner: Disposition*

- "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 Product Owner: Engaging CTLs*

"During the inspection, your firm's management discussed the possibility of using a third-party contractor to perform finished product testing. If you choose to contract with another party to provide release testing activities, then provide in your response to this letter the name and address of this contract laboratory as well as a copy of your quality agreement with the contract laboratory. Additionally, describe your plan for testing active ingredients in each of your finished products distributed to the U.S. market."

# *WL to Product Owner: Ultimate Responsibility*

- "…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 Product Owner: Ultimate Responsibility*

"…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***."

# ‘Two-fers:’ WL to Both

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

# ‘Two-fers:’ WL to Both (cont.)

- Contracted 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.”

# *Conclusions*

- Even in a complex market, everyone is responsible for quality.
- Owners and Contracted Facilities should work together proactively to characterize and control risks to product quality and patient safety.
- A well-drafted QA 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 consequences for patients and your business

# *Questions?*

**CDER OMQ Compliance Policy**

CDEROMQCompliance@fda.hhs.gov