Come on People Now ... Everybody Get Together, Try to Love One Another: FDA Issues Final Guidance on Quality Agreements

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Three and a half years after issuing its draft guidance, on November 22, 2016, the Food and Drug Administration released its final guidance, "Contract Manufacturing Arrangements for Drugs: Quality Agreements."[1] The guidance is not legally binding on industry or FDA and it is limited to human drug, biologic, and veterinary drug companies. However, all FDA-regulated industries should review the guidance, because it reflects the agency's current thinking on the value of quality agreements and its expectations. The guidance is also useful in that it attempts to offer recommendations to industry to minimize quality surprises and to maximize regulatory compliance by building quality into the process early and often. Channeling the Youngbloods 1967 hit, "Come Together," FDA encourages everyone to "come on people now," to "get together," and "to love one another."

This Bulletin summarizes some of the guidance's key elements and recommendations. We will also offer our own observations.

Scope of FDA's Final Guidance

- Applies to all contract facilities, including analytical testing labs, which package, hold, label, test or operate any part of the manufacturing process for active pharmaceutical ingredients, drug substances, in-process materials, finished drug products, combination products, drug constituents of combination drug/device products, and biological drug products
    - "commercial manufacturing does not include research and development activities, manufacturing of material for investigational no drug studies (e.g., clinical trials, expanded access), or manufacturing of material for veterinary investigational drugs"
        - "many of the principles described in this guidance could be applied in pre-commercial stages of the pharmaceutical life cycle"

Contents of a Quality Agreement

- FDA states:

> 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 [Current Good Manufacturing Practices]. In general, the quality agreement should clearly state which party – the owner or the contract facility or both – carries out specific cGMP activities ... 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

1 www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformtion/guidances/ucm353925.pdf

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 inspection.

- FDA recommends quality agreements include:
  - the purpose/scope, which would explain the contract manufacturing services to be provided
  - definitions, which would provide the precise meaning of terms in the quality agreement
  - resolution of disagreements or conflicts, which would explain how the parties will resolve disagreements about product quality issues or other problems
  - manufacturing activities, which would document quality unit and other activities related to production processes, facilities and equipment, materials management, change controls, documentation, and monitoring responsibilities (for purposes of this Bulletin, we will not describe in detail here all of FDA's suggested inclusions); and
  - the life cycle of, and revisions to, the quality agreement|
- The document should describe how parties will communicate information on traceability and prevention of cross-contamination, in cases where the contract manufacturing organization manufactures several different products
- Quality agreements should explain how the contractor will report manufacturing deviations to the drug manufacturer and how deviations will be investigated and resolved in compliance with cGMP requirements
- The agreement should define owner/contract facility expectations for reviewing and approving documents, including standard operating procedures, manufacturing records, specifications, and lab records
  - as noted, the quality agreement should be independent of all other business documents, because the agreement should focus only on quality and compliance, not business or commercial issues

Ultimate Responsibility

- FDA reiterates, through two hypothetical scenarios, that owners and contract facilities are <u>both</u> responsible for cGMP and regulatory compliance
- A quality agreement does <u>not</u> exempt the parties from statutory or regulatory responsibilities
- The application holder remains responsible for ensuring that its products are made in compliance with cGMPs, even if the quality agreement delegates certain manufacturing activities to the contract facility
  - if FDA were to find such problems at the contract facility, regulators "might determine that it is appropriate to inspect the owner," and owners could be in violation of cGMPs because of the failure to oversee contract facilities' manufacturing activities
  - FDA reminds industry that quality agreements should be available for review when the agency conducts establishment inspections
- The sponsor's quality department is legally responsible for approving or rejecting products that are manufactured by their contract parties, including product made for that release
- FDA kept the term "owner" and rejected comments to adopt other terms, such as "contract giver," "contract acceptor," and "authorization holder," which are used in the International Council for Harmonization's Q10 quality systems guideline

AGG Observations

- Companies should review their existing quality agreements to make sure they comply with the guidance
  - consider revisions as appropriate
  - conduct periodic reviews of the agreements to make sure they are current and relevant

- Quality unit representatives should be actively and proactively engaged in drafting quality agreements, along with counsel, in the division of responsibilities and activities

- Presumably, both parties want to work together

  - negotiate in good faith
  - be flexible but, where appropriate, sufficiently detailed in substance and content
    - a quality agreement is an operational document, so don't make it so burdensome that the company cannot operate or inadvertently impose obligations beyond what is required
  - share information in an open and timely manner

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