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Compliance Notes

Quality Agreements for Contract Manufacturers

A well-constructed quality agreement can be an important tool to enable effective collaboration between owner and CMO.

In May 2013, FDA published *Draft Guidance, Contract Manufacturing Arrangements for Drugs: Quality Agreements*, and 37 individuals, companies, and trade associations submitted comments before the close of the comment period on July 29, 2013 (1). The agency has not finalized the guidance document but has implemented an enforcement program based on FDA law and regulations discussed in the draft guidance. The purpose of this article is not to discuss the merits of the submitted comments but to provide perspectives regarding the events leading up to a new enforcement program for CMOs and the sponsor/owner companies that contract them.

Traditionally, the role of the quality agreement has been to divide the responsibility between the contract giver (owner) and the contracted facility (CMO). The cGMP regulations (21 *Code of Federal Regulations* [*CFR*] 210 and 211) require all drug companies (human and animal, pharmaceutical and biological) to have written procedures defining the responsibilities/procedures for their quality organizations (2). The FDA draft quality agreement guidance document offers suggestions/recommendations for using quality agreements as effective tools to support meeting the intent of the regulations.

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The new enforcement program is holding owner companies contracting CMOs more accountable for their CMOs' compliance to the cGMP regulations. As a result, CMOs may find their clients increasingly involved with assessing the state of compliance at the CMO, including increased owner company quality oversight of the CMOs' operations. FDA continues to inspect CMOs in much the same manner as before. What is expected to become common is that the owner firms who contracted the CMOs will increasingly be subject to regulatory actions as a result of cGMP violations at their CMOs. Previously, it was rare that companies that owned the drug products and contracted CMOs were cited for cGMP failures at their CMOs. As the FDA draft guidance states, FDA sees the contracted facility as an extension of the contract giver. This view is supported by cGMP regulation 21 *CFR* 211.22(a), which states "the quality control unit shall be responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company" (2).

Regulatory actions can be useful when they drive a higher level of compliance resulting in fewer violations. FDA believes that holding owners more responsible for their CMOs will result in fewer compliance issues and, ultimately, fewer regulatory actions. An increase in the number of actions such as warning letters, seizures, injunctions, and prosecutions makes drugs appear less safe. The goal of FDA is to ensure public safety and product quality, not to increase the number of enforcement actions.

If compliance issues with some CMOs have

existed for years, why the sudden change in FDA's enforcement policy? CMOs have proliferated because they offer pharmaceutical and biologic manufacturers the means of reducing their manufacturing and labor costs (particularly when the majority of the CMOs are located outside the US) to take advantage of lower cost structures as well as global distribution opportunities. Use of foreign manufacturers as CMOs for the US market, such as manufacturing APIs, has resulted in more cGMP violations as foreign manufacturers adjust to FDA's expectations. The public's concern over drug safety reached new heights with the Heparin contamination problem in 2008 that subsequently led to the passage of the FDA Safety and Innovation Act (FDASIA) in 2012. Sec. 711 of FDASIA, requiring adequate control and oversight of the supply chain, can be expected to impact many CMOs. The proliferation of CMOs globally and the Innovation Act's impact on FDA's resources drives the agency to find more efficient and effective approaches in regulating pharmaceutical firms.

The intense cost pressures, increased competition, tight margins, and insufficient quality systems, among other factors, have led to a higher incidence of noncompliance (e.g., FDA-483s, warning letters, and import alerts) among CMOs than ever before. Most CMOs have multiple clients that contract with them and it is not unusual that owners present with varying levels of expectations related to quality. Furthermore, quality agreements were frequently discussed only after supply contracts were signed.

FDA, in its draft guidance, is reminding owners that they remain responsible for all areas of drug quality, either directly or indirectly. As the draft guidance points out, this was always the intent of the cGMP regulations (21 *CFR* 211.22(a) and (d)).

RECOMMENDATIONS

Read or re-read the draft FDA quality agreement guidance document. This is a document that should be discussed at the highest levels of every CMO and pharmaceutical or biologic company that has contracted

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CMOs, or is considering doing so in the future. This is an excellent time to re-evaluate contracts and quality agreements between contractors and CMOs. Drug manufacturers should not wait for FDA's finalizations of the draft quality agreement guidance to re-evaluate or update their quality agreements. Quality agreements can serve as an effective tool to ensure the appropriate level of quality oversight. The recent increase in enforcement focus has signaled the urgency of revisiting existing, or implementing, quality agreements.

Qualifying CMOs

Some CMOs have in the past placed restrictions on the level of thoroughness of due diligence or pre-contract audits by the manufacturers evaluating them. Due diligence should never just be a limited audit. Check out the CMO's qualifications, past compliance history, organizational structure, quality culture, references, and reputation.

Quality agreements should be a forethought, not an afterthought. The time to implement a quality agreement is before signing a business contract covering supply. Establishing all of the requirements allows mutual agreement regarding what is to be done and the price that is fair for both parties to meet all the expectations.

Oversight

Traditionally, sponsors/owners may not necessarily have visibility to cGMP violations at a CMO that may impact them unless the violations are specifically associated with their drug products. Limiting this awareness of violations at a CMO may limit the sponsor/owner's ability to see and address systemic quality problems. Increased transparency, including access to redacted FDA–483s following regulatory inspections at the CMO will increase the ability of the sponsor/owner to proactively address potential issues.

Taking action now

When FDA considers taking action, they take into consideration what the firm is doing to improve, such as having a continuous quality improvement plan. FDA sees ineffective oversight as insufficient. The more CMOs and owners do to review and enhance quality agreements and compliance oversight, the better position they have to present a proactive compliance stance.

SIX STEPS TO AN EFFECTIVE QUALITY AGREEMENT

The following are six steps owners can take to develop an effective quality agreement.

Step One

Define the scope, including the following:

- Component or details of the service being provided by the contractor
- Name and address of CMO
- Name and address of any subcontractor/suppliers
- Dates and terms of the agreement
- Responsible quality head for owner and CMO
- Detailed description of the component or service, its intended use

in the manufacturing process, and the impact on the final drug product
- Applicable to pharmacopeia, regulatory, environmental, legal requirements
- Specify quality assurance system requirements.

Step Two

Define roles and responsibilities:
- Use a responsibility matrix to clearly define responsibilities of the CMO, the owner, as well as any agreed upon responsibilities shared by the owner and the CMO
- Detailed listing of all the tasks needed to complete the intended scope of operations
- Define owner's responsibilities for conducting routine and for-cause audits and for participation in regulatory inspections
- Define CMO's responsibilities to ensure adherence to cGMP and regulatory requirements and to provide reasonable and appropriate access to owner to enable owner's quality oversight.

Step Three

Define the deliverables:
- Define the required deliverable from the CMO
- Detail the specific testing and specifications required
- Specify CMO quality assurance oversight and certification required to ensure the quality and safety of the deliverables
- Specify the container/closure, transportation, any specific temperature requirements.

Step Four

Define the communication plan:
- Define how the owner and contractor keep one another informed of any issues that may impact the quality of the deliverables
- Define the process for communicating change control, deviations, out-of-specifications (OOS), and regulatory agency inspections to the owner
- The communications plan must be specific about when, how, and to whom any information impacting quality and safety are to be reported.

Step Five

Define the documentation:
- Define the documentation required to support the deliverables including product or service information, certificate of analysis, material safety data sheets, summary of manufacturing, deviations and OOS investigations, and quality assurance statement of compliance to regulations
- Depending on the nature and status of the relationship and quality metric performance, additional documentation may be required, such as batch records and raw testing data.

Step Six

Define metrics for performance:
- Define how the owner will monitor the performance of the CMO. Include, for example, number/frequency of deviations, number/frequency of OOS results, internal audits and regulatory audit performance, continuing process verification, customer complaints and adverse events
- Define timing and frequency of when reviews will be performed and continuously look at performance to proactively avoid loss of a component or service which will cause a disruption to the supply chain and increase risk to patient safety.

SUMMARY

A well-constructed quality agreement can be an important tool to enable effective collaboration between owner and CMO to ensure product quality and regulatory compliance. A quality agreement is ideally constructed prior to entering into a financial supply agreement to ensure that all requirements are fully understood by both parties so they can be adequately addressed as part of the overall business arrangement. The quality agreement does not relieve the owner of responsibilities under cGMP regulations.

REFERENCES

1. FDA, *Draft Guidance, Contract Manufacturing Arrangements for Drugs: Quality Agreements* (May 2013).
2. 21 *CFR* 211.22 ◆