PHARMACEUTICAL ONLINE

Guest Column | March 10, 2017

Examining FDA's New Quality Agreement Guidance

By Bikash Chatterjee, President and Chief Science Officer, Pharmatech Associates

In Part 1 of this two-part article, we discussed how FDA's new guidance for industry *Contract Manufacturing Arrangements for Drugs: Quality Agreements* characterizes the quality agreement as defining and establishing each party's manufacturing activities with regard to maintaining cGMP compliance at each stage. The guidance specifically addresses seven elements that should be included in a quality agreement: quality unit activities, facilities and equipment, materials management, product-specific considerations, laboratory controls, documentation, and change control. Part 1 covered the first two elements; this article will address the remaining five.

While the FDA has elected to limit the scope of the guidance to commercial programs, we will see that industry still requires clarification on responsibilities that occur for a commercialized product after it comes to market.

Materials Management

As the complexity of the production supply chain has increased, so has the importance of materials management. Adding to this complexity is the proliferation of combination products that utilize device components (and intermediates) from multiple countries. The guidance states that a quality agreement should address how the parties will ensure appropriate inventory management, including labeling, label printing, inventory reconciliation, and product status identification (e.g., quarantine). The agreement should also cover how the contract facility will prevent mix-ups and cross-contamination. Again, key considerations in the quality agreement involve how to handle discrepant material and nonconforming product, with specific attention paid to roles and responsibilities as they pertain to sampling, testing, disposition, and supplier management.

Product-Specific Considerations

This section addresses commercial manufacturing requirements that are unique to individual products. The guidance mentions specifically:

- Product/component specifications
- Defined manufacturing operations, including batch numbering processes
- Responsibilities for expiration/retest dating, storage and shipment, and lot disposition
- Responsibilities for process validation, including design, qualification, and ongoing verification and monitoring
- Provisions to allow owner personnel access to the contract facility when appropriate

The section then reminds us to consider how process and product development knowledge will be transferred to the CMO. The challenge with this statement is that it subsumes almost every aspect of the development process, including product specification development, design space establishment, critical process parameters (CPPs), critical quality attributes (CQAs), expected process variability, etc. A clear technology transfer plan to move a mature or legacy process to a CMO does not really belong in the quality agreement. It does make sense, however, to discuss any quality key performance indicators (KPIs) that would be meaningful for the drug sponsor and CMO in the quality agreement.

Laboratory Controls

Whether a sponsor or CMO engages a separate contract laboratory for analytical or microbiological testing, the rules around testing and reporting must be clearly captured within the quality agreement. The guidance specifically mentions five considerations:

- Procedures delineating controls over sampling and testing samples

- Protocols and procedures for communicating all laboratory test results conducted by contract facilities to the owner, for evaluation and consideration in final product disposition decisions
- Procedures to verify that both owner and contract facilities accurately transfer development, qualification, and validation methods when an owner uses a contract facility for laboratory testing
- Routine auditing procedures to ensure that a contract facility's laboratory equipment is qualified, calibrated, and maintained in a controlled state in accordance with cGMPs
- Designation of responsibility for investigating deviations, discrepancies, failures, out-of-specification (OOS) results, and out-of-trend (OOT) results in the laboratory, and for sharing reports of such investigations

Laboratory controls are big part of both process development/technology transfer and deviation root cause analysis investigations. It is important to explicitly define what and how data will be shared between a sponsor and CMO. Some CMOs will defer to summary data, while most sponsors will want all raw data (e.g., chromatograms) in addition to the summary data. Considering all of the data and documentation associated with the laboratory can often reveal data integrity issues, which have been a big area of focus in the FDA's regulatory enforcement landscape.

Documentation

Documentation is one of the most difficult elements to manage with a CMO, since documentation constraints could not be more different between a CMO and a sponsor. A CMO must manage multiple clients, each with their own internal documentation systems and expectations. Consequently, their desire is to find a consistent approach to documentation that will minimize unintended deviations across their client base. The guidance cites several documentation-specific considerations:

- How changes may be made to standard operating procedures, manufacturing records, specifications, laboratory records, validation documentation, investigation records, annual reports, and other documents related to products or services provided by the contract facility
- Defining owners' and contract facilities' roles in making and maintaining original documents or true copies in accordance with CGMP

Establishing product-specific documentation in the quality agreement will help reconcile the expectations between the two parties' QMS, and thus avoid misunderstandings between the sponsor and CMO.

Change Control

Few aspects of the QMS system can cause as much difficulty as the change control process when working with a CMO. Modern change control systems utilize some level of structured impact assessment. The difficulty arises from the ambiguity surrounding what does — and does not — represent a meaningful change of which the sponsor should be notified. Specifically, the guidance cites the following areas where change control must be clearly defined between a sponsor and CMO to ensure cGMP compliance:

- Components and/or their suppliers
- Establishment locations
- Manufacturing processes
- Products or product types that use the same production line, equipment train, or facility
- Testing procedures
- Major manufacturing equipment
- Shipping methods
- Lot numbering schemes
- Container closure systems
- Tamper evidence features
- Product distribution

The issue with all of these areas is in defining clearly what constitutes a minor, major, or critical change. It is recommended that even minor changes — such as replacing a component or piece of equipment with a similar replacement, termed a "like-and kind change" — include a clear definition of what verification is required before implementing the change. In many cases, a sponsor may ask a CMO to simply notify them of any change, instead of requesting to be part of the change evaluation.

Conclusion

The new FDA guidance is a simple one, providing best practices and high-level insight into the components of a quality agreement. However, the FDA missed a chance to truly provide value to the industry by expanding the discussion into the development environment, and by citing their current thinking and industry practice in that domain. The increasing participation of CMOs in the drug development process adds a significant level of complexity regarding roles and responsibilities in managing the two QMS as the program moves towards commercial launch.

One big opportunity missed in the guidance was to include a discussion pertaining to custom quality agreements vs. modifying a CMO's standard agreement. Because CMOs have many clients, anything out of the ordinary has the risk of being ignored or forgotten in routine production. If possible, modifying a CMO's standard agreement will minimize the chances of the sponsor being surprised by the CMO not following the agreement. However, if a CMO's standard quality agreement lacks sufficient content to be useful, the sponsor will have to create a structure from scratch that will ensure compliance with the quality agreement.

About The Author:

Bikash Chatterjee is president and chief science officer for Pharmatech Associates. He has over 30 years' experience in the design and development of pharmaceutical, biotech, medical device, and IVD products. His work has guided the successful approval and commercialization of over a dozen new products in the U.S. and Europe.

Mr. Chatterjee is a member of the USP National Advisory Board, and is the past-chairman of the Golden Gate Chapter of the American Society of Quality. He is the author of Applying Lean Six Sigma in the Pharmaceutical Industry and is a keynote speaker at international conferences. Mr. Chatterjee holds a B.A. in biochemistry and a B.S. in chemical engineering from the University of California at San Diego.