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Guest Column | February 1, 2017

FDA's New Quality Agreement Guidance — What It Says (And What It Fails To Say)

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

In November 2016, the FDA issued new guidance for industry titled *Contract Manufacturing Arrangements for Drugs: Quality Agreements*. This guidance is timely, given the rise of the virtual biotech company in the development landscape. Most development programs now include the support of at least one contract service provider (CSP) for services that vary from early development contract research to commercial manufacturing and analytical support.

One component of CMO engagement that has been hotly debated in the industry is the quality agreement, which the new guidance defines "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." As CMOs assume a much greater share of the development responsibility — evolving into CDMOs — many questions have been raised regarding the content and timing of quality agreements. In fact, the very merit of highly tailored quality agreements has been a point of debate. Let's examine the new FDA guidance with this backdrop in mind.

Limited Scope

First, it is important to note that the new guidance reflects the FDA's current thinking on *commercial manufacturing relationships*, not research and development, and applies to the following categories: human drugs, veterinary drugs, certain combination products, biological and biotechnology products, finished products, APIs, drug substances, in-process materials, and drug constituents of combination drug/device products. The guidance does not cover the following types of products: Type A medicated articles and medicated feed, medical devices, dietary supplements, or human cells, tissues, or cellular or tissue-based products regulated under Section 300 of the Public Health Service Act and 21 CFR Part 1271.

The guidance addresses the relationship between "owners" and "contract facilities," and defines owners as manufacturers of APIs, drug substances, in-process materials, finished drug products (including biological products), and combination products. The term "owner" does not apply to retail pharmacies, drug stores, supermarkets, discount warehouse stores, or other retailers that purchase finished drug products to sell over the counter as a store brand. The guidance defines "contract facilities" as parties that perform one or more manufacturing operations on behalf of an owner or owners.

The big question is: Why would the agency issue a guidance pertaining only to commercial manufacturing? The role of the contract manufacturer has increased over the last decade, expanding to include everything from API design to clinical logistics and pharmacovigilance. Commercial manufacturing is the relationship with which the biopharma industry has the most practical experience, and the content and application of the quality agreement is well-understood between owners and CMOs. It is curious that the FDA chose to limit the guidance's scope to the commercial component when the greatest challenges facing industry lie upstream of commercial manufacturing.

An unintended consequence of limiting the guidance's scope is that it enables CDMOs to use it as an excuse to restrict the sharing of quality responsibilities until the commercial program. This certainly makes the CDMO's job easier, since they have to juggle the differences between each client's QMS. In an era where expedited clinical plans are more the norm than the exception, the need to maintain a practical division of quality responsibilities during development is central to a drug sponsor's/owner's ability to ensure a robust CMC and clinical program.

Lack Of Specificity

Another major problem with the guidance is its lack of specificity. Its discussion regarding the applicability of international best practices standards ICH Q7, Q9, and Q10 tends to remain at a high level, rather than highlighting the key components of the international guidelines that must be addressed. The ICH guidelines do an excellent job of framing the problem, but they stop short of offering practical approaches for applying the concepts they convey. The new FDA guidance would have been an excellent opportunity to provide examples of how these approaches should be articulated within the quality agreement.

For example, the most common risk analysis tools used in risk management activities are the failure modes and effects analysis (FMEA), cause-and-effect matrices, and heat maps. The FDA guidance could have listed several alternative risk assessment approaches in which the agency has formulated some practical experience. For example, the agency has provided feedback to the industry that heat maps should not be limited to the three levels *high, medium*, and *low* because of the natural tendency to push higher risks down into the medium category, based on an aversion to the magnitude of severity associated with a *high* rating. In fact, combination product programs that have a device and design control component will receive swift and direct feedback from the Center for Device and Radiological Health (CDRH) if its design, process, and human factors risk assessment use this construct.

Breaking Down The Guidance Content

On the other hand, the new guidance does provide a general overview of the areas that should be included in a quality agreement. It contains sections on the following elements, as they relate to manufacturing activities:

- Quality unit activities
- Facilities and equipment
- Materials management
- Product-specific considerations
- Laboratory controls
- Documentation
- Change control

We will explore the first two topics from this list at length in the following sections. The remaining topics will be discussed in Part 2 of this two-part article.

Quality Unit Activities

This section should have been the core of the guidance yet comprises only two paragraphs. One of the major challenges with using a CMO is defining how the two organizations' quality units will collaborate and interact with each other. While it is true that the drug sponsor cannot delegate its responsibilities regarding cGMP compliance, the complexity associated with aligning a drug sponsor's quality management system (QMS) with a CMO's is tangible. For example, person-in-the- plant (PIP) is a relationship point where friction can occur between a CMO and sponsor. Notification, frequency, access, and communication rights and responsibilities are elements that should be clearly defined in a quality agreement. A CMO has multiple clients, and each PIP will require hosting and management, adding an extra level of organizational management to the CMO's operation.

Deviation and corrective and preventative action (CAPA) management are other potential areas of discord. Deviations require both the CMO and sponsor to understand the root cause and implications of a process or QMS excursion. Primary responsibility in root cause investigations needs to be clearly articulated in the quality agreement, along with when and how a drug sponsor can participate in an investigation. Often, large pharma and biotech companies have formalized investigation frameworks that must be applied to deviations, while the CMO may allow alternative approaches. The ability to reconcile two distinct sets of requirements is essential to avoid needless downstream disruption of the commercial supply chain. This is another example where limiting the guidance scope to commercial programs represents a missed opportunity by the agency.

In the case of early development programs where technical insight is fluid, it is not unusual for the sponsor to be intimately involved. In later-stage programs, however, the sponsor may have only review and approve authorization, which makes the assessment of the CMO's ability to effectively execute a thorough root cause analysis critically important.

Most CMOs are reluctant to modify their typical deviation template because that could mean constantly revising the document for each new customer it engaged. In addition, the deviation will reside in the CMO's QMS, and the sponsor must decide if it is important to have a corresponding reference within their own system. All of these considerations may require one or both parties to modify their usual processes.

Facilities And Equipment

The new guidance highlights the need to define who is responsible for facility and equipment activities that impact manufacturing operations. This includes defining who will handle facility and equipment qualification and process validation. It also should extend to systems that support the manufacturing operation, including information

technology and automated control systems, environmental monitoring and room classification, utilities, and any other equipment and facilities that must be maintained to perform the contracted manufacturing operations in compliance with cGMP.

However, it would have been beneficial for the agency to also provide some insight as to how a drug sponsor should handle facility and equipment changes after commercial introduction. Establishing a practical and manageable process that will clearly define when and how the drug sponsor will be notified of material changes to the facility and equipment would minimize unexpected excursions downstream. In addition, clearly understanding how the CMO will administer continuous monitoring for Stage 3 process validation is a good framework for the discussion.

We will resume our analysis of the new guidance in Part 2 of this two-part article, examining what it proposes regarding change control, product-specific considerations, lab controls, documentation, and quality and compliance at all stages.

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.