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Following FDA Guidance: Continuous Improvement in an Outsourced Environment

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In May 2013 the U.S. Food and Drug Administration (FDA) released its draft guidance, "Contract Manufacturing Arrangement for Drugs: Quality Agreements," with recommendations representing its "current thinking on defining, establishing, and documenting the responsibilities of each party (or all parties) involved in the contract manufacturing of drugs subject to Current Good Manufacturing Practice (CGMP). In particular, we describe how parties involved in the contract manufacturing of drugs can utilize Quality Agreements to delineate their responsibilities and assure drug quality, safety, and efficacy." (1)

Industry comments that followed called for more detailed direction. Others specifically supported the document's emphasis on drug owner/contractor collaboration. It prompted the industry's acknowledgement that outsourced models have higher risks than traditional ones, and that sponsors and contract manufacturing organizations (CMOs) have shared responsibility for quality. Neither a CMO nor a sponsor can blame a lack of good manufacturing practices (GMP) on missing information from one another.

The guidance should stimulate increased collaboration between sponsors and CMOs, especially with regard to process performance visibility and the exchange of supporting process and quality data, which are essential to continuous improvement and maintaining the state of validation in an outsourced manufacturing environment.

Honing in on the following guidance excerpts begs the question: What practical steps can the industry take to adhere to FDA recommendations?

- "Because the Agency considers contractors an 'extension of the manufacturer's own facility,' both Owners and Contracted Facilities are responsible for ensuring that their products are not adulterated or misbranded (21 CFR 200.10). As amended, the Act also specifies that current good manufacturing practice (CGMP) includes the implementation of quality oversight and controls over the manufacture of drugs…"

- "Owners should monitor and review the performance of the Contracted Facility and identify and implement any needed improvements."

"The parties to a Quality Agreement should include a communication plan that explains how manufacturing deviations will be relayed to the Owner by the Contracted Facility, and how such deviations will be investigated, documented, and resolved." (1)

The product-specific terms section specifies that Quality Agreements should include "responsibilities for process validation, including design, qualification, and ongoing verification and monitoring." And four illustrative scenarios reiterate that "the Owner is ultimately required to ensure that the products are manufactured in accordance with the Act." In its conclusion FDA says both parties "can draw on quality management principles to carry out the complicated process of contract drug manufacturing by defining, establishing, and documenting the responsibilities of all parties involved in drug manufacturing, testing, or other support operations."

The FDA's guidance sets expectations for what Quality Agreements should look like to avoid citations, but to collaborate better and avoid unwanted risk, sponsors and CMOs need to build a better ship, so to speak, to connect their isolated islands. The sponsor typically steers the partner-ship, but a CMO must be fully supportive, coming to the table recognizing that shared responsibility for quality and minimizing risks is mutually beneficial.

What follows is a real-world example used by Shire plc, a specialty pharmaceutical company which engages contractors to manufacture all of its synthetic drugs – including relatively small volume batches of the core products that the company's mission depends upon.

Set Sail with Shared Goals

Sponsors and CMOs both need to be on board with the approach that Continued Process Verification (CPV) should leverage existing processes and systems that work seamlessly – creating simple, flexible practices that anticipate changes related to new products and modified manufacturing processes to existing products as shown in Figure 1:

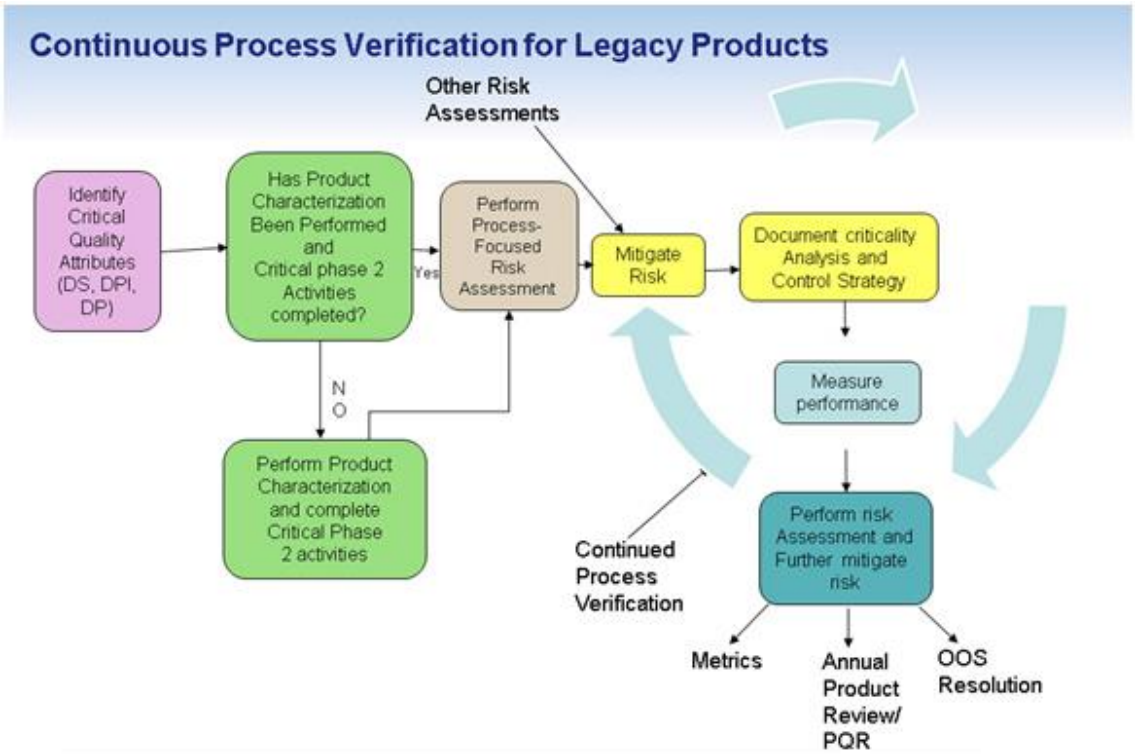

Figure 1: Continuous Process Verification for legacy products manufactured in an outsourced model

A partnership approach that leverages both parties' capabilities can supplement traditional business models to provide a higher degree of assurance that products are available to patients with the required quality. Beneficial shared goals might include:

- Reduce and eliminate out of specification (OOS) incidents
- Minimize process variability
- Meet regulatory requirements and commitments.

To monitor progress toward shared goals in a seamless partnership, a "plant-in-plant" approach applies an oversight model with three governance bodies including a steering committee, a more near-term strategic committee and a day-to-day tactical staff. These committees establish metrics to evaluate not only throughput, but other elements that impact the way they do business together related to people, plant, process, technology and risk. In an inverted pyramid fashion as shown in Figure 2, team representatives from the sponsor and CMO meet on a regular, predetermined schedule.

Figure 2: The plant-in-plant approach in an outsourced environment helps facilitate CPV.

The operational team(s) works together on a tactical level to make improvements and conduct batch-level investigations. The tactical execution team then focuses on resources to ensure funds, people and scheduling adjustments are in place. The technical review committee evaluates product performance and existing opportunities on a monthly basis. Members determine what projects are needed to reduce variability in product performance. Finally, the joint executive steering committee approves these projects and resources and provides strategic guidance.

In the best relationship – especially when one owner sponsors a large portion of one CMO's total products – the sponsor may have a specialist on site in the CMO's plant to help review batch records in parallel and ultimately increase batch throughput, or a software platform will be in place that enables secure data exchange and visibility into process performance. In a well-integrated partnership, robust discussions focus on standardization, joint programs and rewards, and patient testimonials that inspire

all teams. Even human resources groups work together to ensure cultural alignment and complementary employee skill-sets.
Within a framework such as the one described, sponsor and CMO partners can prioritize which improvements and shared goals to target – from increased compliance profiles, line item fill rates and supplier quality indexes to decreased conversion cycle times, customer lead times and batch release cycle times.

CPV for Traditional vs. Quality by Design Products

CPV involves ongoing assurance that the process remains in a state of control during routine production. For legacy products, which most sponsors outsource today, CPV starts at "stage 3".

This presents a challenge in knowing where to start. What does the sponsor already know of the product's history? For CPV, stage 3 includes: 1) assessing process capability with respect to customers' needs 2) understanding true process variability 3) increasing understanding of process robustness and 4) confirming the adequacy of the control strategy.

Approaches similar to those used for new products under Quality by Design (QbD) – where quality is designed into the process – can be leveraged for traditional products to enable CPV, with differences shown in Table 1.

Traditional Product Deliverable	QbD Product Deliverable
Development history report	Criticality analysis and control strategy documents
Process capability-based specifications	Design space-based specifications
Annual product review and product quality review	Monitoring protocols and reports producing periodic, cumulative, comprehensive product reviews
Process validation protocol and report including enhanced sampling	Process validation protocol report and sampling strategy

Challenges inherent to CPV for traditional products involve understanding product, process and material properties. Remember that for QbD products, technology enabled analysis is built-in. Large volumes of data for legacy products, however, are often stored in disparate data sources (including paper records) and are difficult to obtain in "relevant time," i.e., a time frame sufficient to allow appropriate action before the next occurrence. In addition, product improvements can often require implementing changes in a complex supply chain across multiple markets.

Sponsors can establish systems that work at CMO locations or for insourced manufacturing environments with traditional and QbD products both under the same Quality system. A governance document used for QbD can become the Quality agreement. Activities such as risk assessment fall under the change control and other Quality systems. Monitoring protocols and reports issued periodically (e.g., quarterly) can be used to build annual product reviews (APR).

If implemented according to QbD principles, CPV can increase value and performance through the traditional product lifecycle as teams continue to develop product and process understanding. Starting with input from development studies and product characterization reports, what these sources reveal about variability and interactions between inputs and process parameters helps to determine Critical Quality Attributes (CQAs) and identify acceptable ranges for those inputs and parameters – including which ones are critical and which are non-critical. Any attribute that cannot be characterized as noncritical to quality is deemed "potentially critical." At the point when product understanding has

improved, the team can reassess the “potentially critical” parameters. With these steps, developing a monitoring plan as part of CPV helps minimize risks by understanding and identifying drivers of variability.

Challenges still exist, especially related to data availability so that sponsor/CMO systems can communicate effectively and efficiently while protecting their other clients’ confidential information. Breaking down cultural, organizational and technology barriers and aligning processes are essential, so the right enabling technology platform needs to facilitate collaboration across organizations to ensure that improvements are identified and implemented – sometimes with shared incentives for both parties. By leveraging available systems to learn more as an industry, we can help sponsors and CMOs define common standards and share best practices – charting a fresh course on this new frontier encouraged by FDA’s guidance.

Reference

1) FDA, “Guidance for Industry. Contract Manufacturing Arrangements for Drugs: Quality Agreements,” May 2013