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# CMO Quality Management Insights

The pharmaceutical industry and the creation of new drugs is expected to continue growing at a steady rate over the next decade.[1] To keep up with this growth, many companies are turning to contract manufacturing organisations (CMOs) to assist with product manufacturing. A key benefit CMOs provide is to maintain a manufacturing footprint, and the skilled talent needed to support product manufacturing. This reduces the need for the product owners to carry these costs or delay progress of their drug development until these resources are directly available. Often CMOs can also assist in bringing products to market more quickly by providing assistance on process and analytical development aspects as well. However, as with most things, the benefits of CMO use also come with some risks.

A CMO can be an important party in the product supply channel. The product sponsor is expected to ensure the CMO is part of a robust supply channel that minimises the risk to patient safety and product supply.[2] To meet this requirement the product sponsor establishes and maintains a diligent quality management strategy for oversight of the CMO. Outsourcing the manufacturing activity does not alleviate the product sponsor from responsibility for the quality and safety of the drug product. This holds true for product manufacturing whenever the product is intended to be consumed by a patient; clinical trials or post-market approval. As outsourcing has become a more common practice, regulatory authorities have evolved their expectations for contract manufacturing oversight.

**Regulatory Expectations**

Regulatory authorities worldwide understand the need for use of contract manufacturers. This is evident in the guidelines and directives that directly address the expectations for quality oversight of a CMO. For example, the European Commission devotes the entire GMP Chapter 7 to Outsourced Activities and outlines the activities of Contract Giver (Product Sponsor) and Contract Acceptor (CMO).[3] ICH Q10, contains expectations for oversight of outsourced activities.[4] Additionally, the ICH Q9 (R1) updates include the expectation for integrating quality risk management activities into industry operations. That includes the application of QRM to oversight of outsourced activities.[5]

The regulatory authorities have also reiterated that outsourcing does not mean the product sponsor can outsource responsibility for the quality and safety of the drug. Here are two examples of statements the USFDA has made in warning letters related to use of contract manufacturing and responsibilities:

- **Responsibilities as a Contractor**
  FDA is aware that many drug manufacturers use independent contractors such as production facilities, FDA regards contractors as extensions of the manufacturer. You are responsible for the quality of drugs you produce as a contract facility regardless of agreements in place with product owners."[2]
- **Use of Contract Manufacturers**
  FDA is aware that many drug manufacturers use independent contractors such as production facilities, FDA regards contractors as extensions of the manufacturer. You are responsible for the quality of your drugs regardless of agreements in place with your contract facilities."[6]

More recently a warning letter was issued to a sponsor company utilising a CMO that received a warning letter. The company continued to distribute drug products from their CMO after the CMO received the warning Letter. Specifically, the warning letter captures the following points:

- "You also failed to have adequate supplier qualification procedures to ensure that the drug products received were manufactured in compliance with CGMP prior to being distributed."[7]
- "You received and delivered into interstate commerce products that were found to be adulterated."[7]

These statements represent the current thinking of regulators as regards the responsibility for ensuring the quality of the drug products manufactured at CMOs on behalf of product sponsors. It is clear that this is a shared responsibility and both parties are responsible for ensuring drug products are produced under cGMP. Both parties must have a focus on patient safety.

**Importance of Proper Qualification and Oversight**

The key to avoiding negative regulatory actions when utilising a CMO is in the initial qualification activities and ongoing quality management engagement with the CMO. Here are some recommendations based on best practices encountered over years of personal experience. The CMO should be qualified through an onsite audit to ensure the facility and staff are capable of manufacturing, testing, storing, and distributing product in a manner consistent with cGMP. This initial qualification should also consider the capabilities of the CMO to control contamination, including cross-contamination from the other products being manufactured in this the same facility. The initial qualification activity completed prior to agreements to initiate work with the CMO.

The initial qualification audit is based on a sample of activities available for review during the agreed time. This may not allow enough time to capture all aspects of the controls needed for ongoing compliance. Therefore, it is also important to have ongoing quality management engagement with the CMO. The expectations for quality performance, responsibilities and communications should be captured in a quality agreement between the CMO and product sponsor. It is essential that each party conduct a comprehensive review to ensure the agreement captures the specifics needed for the product under consideration. Once the agreement is in place, ongoing engagement with the CMO is needed to ensure the product sponsor's requirements are fulfilled as expected. The expected communication plan and governance should be outlined and agreed in the quality agreement.

It is common for commercial product sponsors to have formal qualification and quality oversight plans with CMOs

already in place prior to commercialisation. It is less common for those product sponsors entering clinical trials. According to FDA's guideline for cGMP for Phase 1 investigational drugs and EC GMP Annex 13 covering investigational drugs, even at the clinical phase 1 stage these products must be produced under a state of control that ensures these products meet the safety, purity, identity requirements needed for use in patients.[8,9]

Even in the early phases of clinical trials, it is important that product sponsor must have qualify and maintain quality oversight engagement with the CMO. Unfortunately, failure in this area could result in the product application not being approved due to the CMO site failing the GMP inspection.[10]

This is not something to be learned at the application stage. Starting early with qualification of any facilities performing manufacturing on behalf of the product sponsor is essential along with continued oversight to stay on track.

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