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4 Key Considerations When Engaging A New GMP Contract Service Provider

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Integrating a contract service provider (CSP) as part of a supply chain to bring a product to market is a critical decision that impacts business performance and carries regulatory and compliance risk. The selection considerations can vary substantially as your program moves from early development contract research to commercial manufacturing and analytical support. This article explores what is important when establishing an effective relationship with a CSP as the program moves from product and process design to commercial manufacturing. (For a discussion of essential considerations when establishing a relationship with a CSP for early development programs, read *Harmonizing Quality Management Systems In Early Drug Development*.)

Shifting Success Criteria

As a program evolves to the later stages, the considerations involved in identifying and working effectively with contract manufacturing organizations (CMOs) and contract laboratories shift to a regulatory and compliance context and execution effectiveness. The following four areas are important to address when establishing an effective sponsor-CMO relationship.

Analytical Method Development / Transfer

If a CMO is engaged to manufacture and test any portion of the manufacturing process, the analytical method transfer is central to developing a robust control strategy and, post-approval, ensuring a robust commercial process. The United States Pharmacopeia chapter USP <1225> — Validation of Compendial Procedures — defines four categories of methods that must be validated, as follows.

- *Category 1* – analytical procedures for quantitation of major components of bulk drug substances or active ingredients (including any preservatives) in finished pharmaceutical products.
- *Category 2* – analytical procedures for determination of impurities in bulk drug substances or degradation compounds in a finished pharmaceutical product. These procedures include quantitative assays and limit tests.
- *Category 3* – analytical procedures for determination of performance characteristics (i.e., dissolution, drug release).
- *Category 4* – identification tests.

The USP does not differentiate between a method developed internally or externally being transferred internally or externally. In either case, there are several key steps to help ensure the method transfer exercise is an effective one:

- If possible, use the same make and model of equipment at the CMO as was used for method development. Some may argue that one high performance liquid chromatography system is the same as another, but the reality is there are differences between manufacturers and models. Understanding that the method may have to be modified to accommodate these subtle differences will go a long way in avoiding unexpected results. Retention time drift, for example, can be influenced by slight differences in instrument stability.
- Ensure that the acceptance criteria for comparability are meaningful. Testing material against a specification does not give you a predictive component for comparison. Target values, including tolerance or confidence intervals, will more accurately describe the performance of the two methods and systems.
- Ensure the validation protocol meets the requirements of ICH Q2B (Validation of Analytical Procedures: Methodology).
- Agree up front what data will be shared and reviewed prior to executing the protocol. Doing so will ensure that both the sponsor and the CMO are on the same page should an investigation be necessary.

For biologic products, it is not uncommon for the drug substance and drug product to be manufactured at different CMOs. In some cases, the final drug product testing will be done at the drug product CMO or, quite often, it is carried out at the drug substance manufacturer to avoid having to do two analytical method transfers. Capturing the roles and responsibilities for managing the sample and testing logistics, data review, and product release within the quality agreement is an effective way to ensure that the sampling and testing are consistent and that there is no confusion if any nonconformance is encountered.

Scale-Down Model / Control Strategy Development

Scale-down models are commonly used to execute process characterization studies as well as to screen raw materials and to conduct investigations in support of manufacturing operations for biologic processes. At a minimum, if designed correctly, these models will provide the means for identifying any critical process parameters (CPPs) and critical material attributes (CMAs) and establishing the final design and control space for the manufacturing process. More importantly, they are the core component of developing a defensible control strategy across the process train for a product and are defined as the key output from Stage 1 of the process validation life cycle. For biologics, it is a requirement of the FDA's biologics license application (BLA) process that the scale-down model be validated. For small molecules, there is no requirement for validating the scale-down model, but the same requirements for developing a defensible control strategy remain.

There are several challenges typically encountered when defining the control space with a CMO. The first is how to fully align the CMO's policies, practices, and definitions with the sponsor's without creating a gap in the sponsor's QMS. All CMOs must balance their policies and procedures across new and legacy product programs. Some larger, fully integrated CMOs manage as many as 400 active clients across their networks. As a result, some CMOs may be reluctant to fully align their formal policies and procedures because of the potential for creating noncompliance for legacy programs. One practical way to manage this divergence is to incorporate program-specific elements into a program master plan document such as a process validation master plan. Since the challenges related to concepts around the 2011 process validation guidance[1] and 1987 guidance apply at the pre-commercial stage, this will allow the sponsor to establish a defensible plan without compromising the CMO's ongoing program.

The second challenge often encountered with a CMO is ensuring that its technical team has the experience and expertise to design and analyze robust orthogonal experimental studies to determine the design space and identify any CPPs and CMAs. The level of scientific rigor required to satisfy the chemistry, manufacturing, and controls (CMC) requirements for a

modern FDA new drug approval (NDA) or BLA filing are considerably higher since the issuance of the 2011 process validation guidance. If a CMO has been engaged to lead and deliver the final control strategy, it is important to have an expert with a strong foundation in the application of experimental design and statistical analysis for process design to ensure that the proposed studies and measurement criteria will meet the agency's expectations within the development report and regulatory submission.

Data Management And Privacy

Data management and IT integration have taken on renewed importance since the Drug Quality Security Act (DQSA) was signed into law in November 2013. This new law harmonizes pedigree requirements across the U.S. and was designed to deploy in phases across the supply chain, thereby establishing a cohesive history of all transactions and chain of custody.

In 2017, CMOs and drug manufacturers must comply with their portion of the serialization and reporting scheme. Most CMOs have active programs to meet the requirements of the law, but if a CMO is intended to be the commercial manufacturer it is important to ensure that the required reporting will be in place. Over the long term, the sponsor may require visibility into the CMO's operations as it relates to its product. Many CMOs opt for cost-effective enterprise research planning (ERP) solutions versus heavyweight solution such as SAP or Oracle because of the ease of installation and the degree of functionality. However, those solutions may make it more difficult to fully comply with the law's requirements without some retrofit. Beyond the impending DQSA requirement, any multinational corporation will likely have some level of business continuity strategy in place. Ensuring the information can seamlessly be transferred to a secondary site is an important consideration when looking at a CMO's IT architecture.

Looming on the horizon for any organization, including CMOs with CRO capability, is the European Good Data Protection Regulation (GDPR), slated to go into effect in 2018. This law will impact any company looking to do business in the European Union and has greatly expanded the fines associated with noncompliance, up to 4 percent of an organization's worldwide revenue. It is important to ensure that your CMO has a clear understanding of the steps needed to comply with this new law before moving into any program in the European Union.

Regulatory Experience

For a CMO that has a role in the development of the product and process, the CMO's ability to prepare and support a pre-approval inspection (PAI) can be a major consideration. Most sponsor companies will prepare for the CMC and clinical review of the NDA/BLA/MAA (marketing authorization application) submission and will have the advantage of all feedback and communication with the regulatory agencies prior to the PAI. Using this knowledge to prepare a CMO is critical to a successful outcome.

A CMO's ability to participate effectively during an inspection as it pertains to the technical development of the process and control strategy is a relatively new phenomenon over the last few years. Understanding the strengths and weaknesses of the CMO's team in presenting the information and answering questions should be a primary component of the PAI readiness activities. The context for the PAI readiness assessment will be expanded, moving beyond basic GMP preparedness into the CMC component and, if the CMO has CRO capabilities, can include the CMO's ability to demonstrate compliance with GCP guidelines. Establishing these expectations is critical during the quality agreement definition and development to ensure that both parties, each of which has much to gain and lose, are clear about their roles and responsibilities.

Managing A Complex Partnership

The role of a CMO has evolved dramatically over the last decade from a simple service provider executing a well-known process as defined by the drug sponsor. It is now a complex partnership where the roles, responsibilities, and expectations between both parties must be laid out as soon as possible in the engagement process. A CMO's ability to effectively defend the CMC-related development work and satisfy impending legal requirements related to information management and privacy has the potential to greatly impact a sponsor's commercial development and supply chain.

References:

1. *Guidance for Industry – Process Validation: General Principles and Practices*, FDA, January 2011.

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.