CDMO EVALUATION

CMC And Quality Considerations When Engaging Your CDMO

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Deciding to use a CDMO to support your drug development program adds complexity and risk if the right partner is not identified and engaged. Before pursuing an outsourcing strategy, it is essential to define what processes will be kept in-house and where your CDMO partner will take the lead. This partner can be used to either spearhead or support several areas in the drug development road map, from the earliest stages in drug development through process characterization, tech transfer, and analytical method development to post-approval clinical commitments.

The evaluation criteria should encompass the CDMO's management team and senior leadership, under several important aspects: internal CMC (chemistry, manufacturing, and controls) support capability and expertise, project management capabilities, quality assurance, quality management systems (QMS) and supportive programs, regulatory affairs support capabilities, equipment qualification and process validation expertise, technology and manufacturing capability and capacities, and company culture, mission, and values.

CMC AND QUALITY ASSURANCE FRAMEWORK

Understanding that a drug sponsor's requirements for a CDMO partner will change as a product moves through its clinical program toward commercial manufacturing is fundamental when evaluating a CDMO's ability to support your program. Consider that this is a long-term relationship proposition that could easily span 10 years or more. How a CDMO addresses two critical areas — CMC support and quality assurance — can often dictate how effective a CDMO can be in supporting and accelerating the timeline for the drug sponsor's drug development program through commercial manufacturing.

Evaluating a CDMO's quality and operations systems and personnel in isolation will not provide a complete picture of the metrics for a successful relationship. The reality is that the drug sponsor's infrastructure and systems must interact with the CDMO's systems to effectively leverage their expertise and capabilities. Including this aspect as part of the assessment exercise will help prevent any issues going forward.

CMC CONSIDERATIONS

Specific considerations as they relate to a drug sponsor's ability to effectively utilize a CDMO for drug development are as follows:

Drug Modality Experience

The CDMO's ability to understand the critical operations related to the functionality of a drug's modality can impact the level of oversight and participation required by the drug sponsor. This element alone can foretell potential challenges as the program moves to commercial manufacturing. For example, basic knowledge of a unit operation's impact on process reproducibility is a good indicator of how an organization can integrate process experience that is not routine. If an operator can clearly convey that they understand what is critical when disassembling, cleaning, and reassembling spray guns and tips for a simple oral solid dose (OSD) drug development process, or a more sophisticated spray drying or Würster process, that is a good indication that a CDMO has learned from past mistakes and has taken proactive measures to prevent any future problems.

Process Characterization Expertise

The level of understanding that the technical staff commands regarding identification of critical process parameters, raw material characterization design of experiments (DOEs), and statistical analysis will provide insight into the CDMO's ability to support and provide the data required to support an NDA or biologics license application (BLA) filing. You should understand their approach to protocol development, how they handle sampling plan justification, and drug sponsor justified characterization requirements, such as demonstrating content uniformity. A CDMO with a working knowledge of process characterization will be more vigilant as you move to managing routine commercial variability challenges.

Method Development Expertise

How a CDMO approaches method development or method transfer provides insight into their understanding of the sources of variability that can be an issue with late-stage clinical supply and commercial manufacturing. The rigor and specificity of the method development and transfer process is a good indicator of the kinds of issues the CDMO has anticipated and integrated into its routine operations. For example, confirming that method development is not performed on QC equipment — a simple evaluation criterion — is a small but important indicator of future potential laboratory issues.

Data Management

The flexibility that a CDMO employs when in the development phases vs. commercial operations will indicate whether a drug sponsor can realize some timeline acceleration from early access to data during process development and gives you an indication of their commitment to data integrity. The maturity of the systems and processes a CDMO employs is a good sign that they understand the potential issues that could be encountered in the later stages of development and that could impact your filing and commercial manufacturing.

3 Stages Of Process Validation Framework

One of the challenges CDMOs face is their ability to support both development and legacy commercial products. Try to understand how organizations implement the FDA's 2011 process validation requirements, how they accommodate legacy commercial products

approved prior to 2011, and how they deploy their Stage 3 CPV (continued process verification) program. This will indicate how prepared they are to conduct the studies that are necessary to support all three stages of process validation. This is an area where the drug sponsor may have to take on additional responsibility. The CDMO should have a defined framework or process for accommodating constantly evolving expectations from regulatory bodies without impugning their existing commercial programs.

PHASE-APPROPRIATE QMS

A phase-appropriate QMS speaks to the fact that the level of quality oversight and involvement evolves as a drug moves through the development process. While a complete GMP assessment should be performed as part of any CDMO evaluation, there are several areas that give indications that a CDMO could become a successful commercial partner.

Training And Competency Assessment

Training is one of the core pillars of a robust GMP framework and is one of the primary contributors to developing a quality culture. CDMOs are constantly confronted with new processes and programs as they expand their customer base. Effective training programs translate to lower systemic excursions and that equates to a lower cost of poor quality (COPQ). CDMOs should be able to articulate how they utilize their training programs to accommodate new processes, novel technologies, and drug modalities on the floor. In addition, a clearly defined job skill matrix for every position in the organization should be in place. A review of the training records should reveal that all training is combined with some level of competency assessment. Most importantly, there should be a clearly structured on the job training (OJT) framework. An effective OJT program ensures employees can translate the intent of each GMP document into practice and understand how they relate and support each other. Capturing the learnings as the program moves along the drug development process will pay dividends as the program expands to commercial manufacturing.

Deviation System

The deviation system captures excursions and non-conformances across the drug development life cycle. How a drug sponsor’s quality organization will participate and interact with the CDMO’s QMS is an important facet to define at each stage of the product’s development but is especially true for the deviation system. The rigor of all root cause investigations, the investigators’ training and preparation, and the processes used are important components to assess. The specifics of the interaction may be captured in the quality agreement or may be partially captured in the QMS. In reviewing and approving all deviations, expect the drug sponsor’s role to escalate as the product moves to commercial manufacturing, which could impact the program in terms of time and cost.

Data Integrity

Ensuring the integrity of the data generated by a CDMO is paramount to a smooth drug development partnership. A CDMO should have a mature data integrity program in place, especially in the laboratory. The staff should be able to define these processes, why they

are required, and how they fit together. The quality group should have a framework for routine data integrity audits, not only in the lab but also on the shop floor. Even during early development, there should be a process defined for capturing GMP data as part of their GxP IT management system.

Quality Culture

Characterizing an organization's culture is not always simple. A culture of quality means the organization does the right thing even when no one is watching. A drug sponsor is placing responsibility in the CDMO's infrastructure and systems but also trusts that the organization will do the right thing, even when they are not present on-site. Several aspects influence a culture of quality, such as leadership's commitment to quality, empowerment of employees to address quality issues, the technical staff's awareness of factors that affect product quality, and structured programs to celebrate quality achievements. Interviewing staff and gauging their level of engagement and their leadership's engagement are good ways to determine how commercial issues will be handled and if the CDMO will be suitably prepared for pre-approval inspection (PAI) and commercial manufacturing.

Change Management

Ensuring that a clearly articulated change management framework is defined and in place as a drug sponsor's program moves through the development life cycle is critical. A common definition of minor, major, and critical changes, and the level of interaction and approval needed at each level, will go far in ensuring there are no unpleasant surprises downstream. A CDMO must juggle multiple programs and should be able to plainly articulate how it manages multiple program changes on process and test equipment and on operational and quality systems. It is important to recognize that any deficiency in a different drug development program can derail your program if it results in enforcement by a regulatory agency.

AVOID MISTAKES AND LOST TIME

Identifying the right CDMO partner can be a complex undertaking, but lack of structure can lead to mistakes and lost development time. Recognizing that the CMC and quality expectations will change as your program moves toward commercial manufacturing is key to your assessment. It's important that both drug sponsor and CDMO work together efficiently to lower the overall risk for both parties and ensure that the foundation for key systems and processes is plainly defined.

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