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The Right Stuff: Making the Transition from Development to Commercial Manufacturing with Your CMO

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The emergence of virtual biotech, specialty drug delivery companies and the increase in the number of in-licensed and collaboration development programs has spawned a new generation of Contract Manufacturing Organizations (CMOs) offering services spanning almost every aspect of the drug development lifecycle. Evaluating and selecting a CMO is a seminal decision that affects the overall success of a development program. However, the factors that make a good development partner may not always translate to the ideal commercial partner. What is the best way to sift through to the essential elements that align the process and promote the partnership? This article uses a recent case study to illustrate some specific areas at risk that can impact a drug sponsor's regulatory risk profile and on-going commercial operations as a drug sponsor's development program transitions to commercial launch.

Project Background: New Drug Application

A U.S.-based drug sponsor had in-licensed a proprietary platform from a European Clinical Research Organization (CRO) for controlled release drug delivery. As a virtual organization, the actual product development work supporting the NDA was performed by the CRO. The final product was to be manufactured in a pre-filled syringe (PFS) as the drug product primary container. In addition to handling the product development and non-clinical studies, the CRO selected all suppliers, and identified and selected the drug product CMO. The drug sponsor was responsible for the clinical program design and administration and for engaging the final combination product CMO. Eventually, however, all responsibility would be transferred to the drug sponsor at the time of NDA submission.

CMO Evaluation and Selection

The CRO had outsourced its supplier qualification auditing responsibilities to a third-party consultant. The consultant established a formal qualification framework for all of its suppliers that was quite rigorous from a USFDA GMP perspective. Internally, the CRO did not have extensive experience with combination products and did not evaluate whether the candidate CMOs were familiar with or capable of supporting 21 CFR 820 - or at a minimum the corresponding elements as defined in 21 CFR Part 4. In the end, the CRO selected a smaller CMO that had experience in aseptic product development but had not supported a commercial product or PFS. Several years prior to the NDA submission the CMO in question had received a Warning Letter from the FDA that required significant remediation to remove. Ultimately the FDA did deem the remediated operation as GMP compliant.

Commercial Readiness for a Complex Product

The complexity of this combination product was significant, as were the corresponding CMC requirements for the NDA. As part of the readiness activities the following key points emerged as points to consider when transitioning a program at a CMO from development to commercial readiness (*Figure 1*).

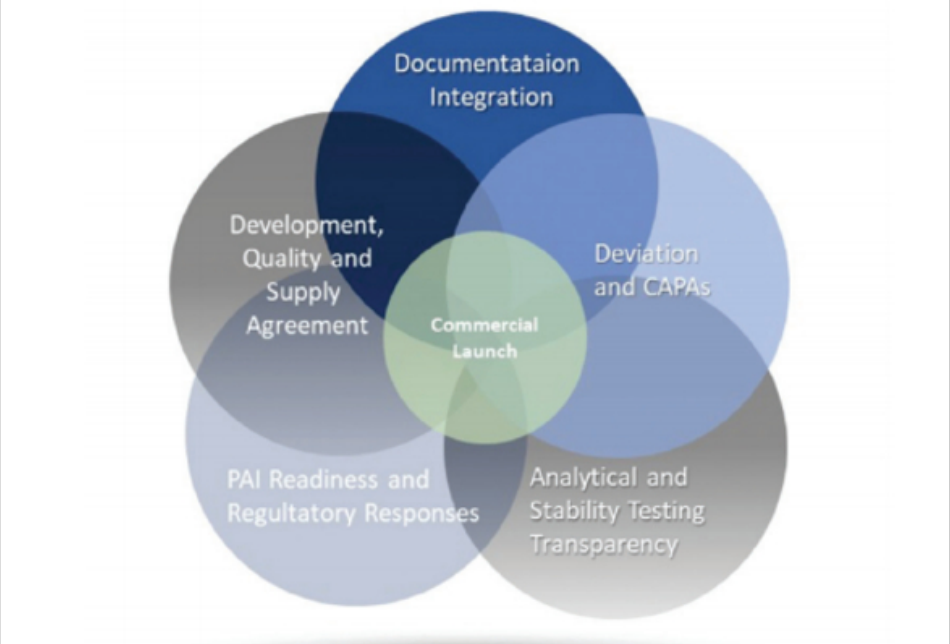

Figure 1. CMO Commercial Transition Focus Areas

Documentation Integration

As you prepare to move to the commercial product launch phase there are many key decisions to make between you and your CMO to manage the uncertainty. One basic reality of all regulatory submissions is that the specifications for raw material, bulk drug, drug product, and finished combination product will not be confirmed until after the FDA reviews the submission. As it pertains to this product, the specifications that were submitted were draft and reflected the development CRO's proposed limits. The specifications, however, had not been entered into the CMO's Quality Management System (QMS). As the drug sponsor began planning for manufacturing process performance qualification (PPQ) lots, this integration activity became rate-limiting in terms of the commercial launch schedule. In addition to the specifications the CMO had outsourced some of the pre-filled syringe (PFS) functional testing to an external testing lab without prior authorization from the drug sponsor. Consequently, the equipment needed to be purchased and qualified at the CMO; the method transferred, and revalidated, and comparability demonstrated at the CMO. This became another rate limiting step in the commercial readiness. Simply ensuring there were adequately trained personnel to execute the testing at the site also became an issue. The same issues arose with Container Closure Integrity Testing (CCIT). Again, unbeknownst to the drug sponsor, the CMO had outsourced the testing to a contract service laboratory and the method needed to be transferred to the CMO. All of these issues were identified during the NDA preparation; however, it took more than three months to complete these activities with the CMO. Finally updating the Master Batch Record to reflect the proposed manufacturing lots sizes, yields etc., was not started until after submission of the NDA and took almost three months to move through the CMO's documentation system.

These risks could have been mitigated by conducting a CMC-based gap analysis at the CMO, and discussing with them a practical schedule and alternatives in support of the commercial launch plan.

Deviations and CAPAs

This CMO had been audited by the USFDA, the drug sponsor, and the Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom (UK), utilizing a systems-based audit. So, the assumption was that the basic QMS elements were in place and compliant. Even so, when you ask a CMO to do something with which they have limited experience, keep in mind that the likelihood of issues arising can be great. During development the drug sponsor - or in this case the development CRO - was available to provide guidance as to the execution of these novel processes. As you move toward commercial launch the primary responsibility for execution of these systems shifts to the CMO, with notification to the drug sponsor. If metrics for performance and involvement have not been finalized as part of a Quality or Supply Agreement, then the likelihood of unforeseen issues goes up markedly. In this case, the root cause analyses related to deviation investigations and the recommended CAPA remediation and measurement criteria were inadequate and inconsistent with the data observed. Secondarily the time to complete the deviation and notify the drug sponsor was unacceptably long (>6 months). This could be partially attributed to the lack of a performance definition in the development agreement, and the CMO's unfamiliarity with the more sophisticated processes and testing related to this

complex drug product. This is another reason why the drug sponsor needs to focus on the true capabilities of the CMO and its personnel when making the jump to commercial.

Analytical testing and Stability Testing Transparency

This product included a month-long controlled-release product presentation. As such, the FDA requested the development of an *in-vitro* method for product release that had adequate discrimination to measure the drug dissolution. It is part of the regulatory submission review to receive information requests from the FDA for additional data or clarification. In this case, the agency mandated a shift in the overall dissolution endpoint for the method. The CRO was able to modify the method to accommodate this request, but transferring the method, validating and training the CMO analysts to perform the modified the method was again, a gating process to commercial launch. Complicating matters was the CMO's reluctance to share the integrated, transferred methodology that had been placed into their system with the drug sponsor. Consequently, the adopted method at the CMO lacked the necessarily granularity regarding equipment setup and suitability testing to preclude testing errors. These errors were flagged during the Pre-Approval Inspection by the FDA and resulted in a 483 observation that needed to be addressed prior to launch.

Defining the roles and responsibilities within the protocol or development agreement before initiating a method transfer is essential to ensuring these simple issues do not become an impediment to FDA approval and commercial launch.

Pre-Approval Inspection (PAI) Readiness and Regulatory Inspection Responses

The drug sponsor attempted two PAI readiness mock audits. In both audits the CMO was distracted by a new client who was on-site to manufacture a batch so, the site's SMEs were not readily available to answer questions, rendering the readiness exercise ineffective. As a result, the drug sponsor conducted a risk assessment of all activities related to PAI readiness with a significant number of the higher risks from a compliance - or an operational risk perspective being assigned to the CMO.

Many of the observations identified during the actual FDA PAI could have been effectively mitigated prior to the FDA's arrival but instead impacted the overall commercial approval timeline and added considerable risk to the validity of the PPQ batches. Unfortunately, the CMO decided to respond to the observations without allowing the drug sponsor to participate in the proposed remediation plan until it had already been submitted. The agency was not satisfied with the proposed responses and mandated a follow-up meeting at the district offices to review their inadequacy. Again, the lack of defined responsibilities impeded the drug sponsor from being able to intervene to avoid this additional risk to the program.

Development Agreement/Quality Agreement/Supply Agreement

At the time of NDA submission, the drug sponsor was still operating under a development agreement. A basic quality agreement had been agreed to but it did not reflect many of the details associated with the transition from a development to commercial organization. Simmering in the background was the basic disconnect between the CMO and the drug sponsor to agree on a binding duration. Based upon the product forecast, the CMO was capable of supporting commercial manufacturing for approximately three years. However, the CMO was looking for a much longer duration, extending it and adding capacity to the plant. Rather than resolve these fundamental differences the drug sponsor chose to operate under the development agreement.

Conclusion

Transitioning from a development partner to a commercial partner is a major shift in responsibility for a CMO. The reality is, most CMOs have many clients they are attempting to manage on a daily basis, and their ability to respond quickly to required changes to a program resulting from regulatory review is a matter that should be discussed. The discussion should define the roles and responsibilities in each task. A RACI[1] framework is an excellent means of capturing the details of what to expect before embarking upon these mission-critical activities. Lastly, each participant must have some skin in the game. In this case, moving from a development agreement to a Supply Agreement could have provided the framework to make sure that performance expectations were well understood by both parties, and reduced the potential risk of these typical, but disruptive, activities in bringing the approved product to market.

References

1. https://en.wikipedia.org/wiki/Responsibility_assignment_matrix

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