Preparing For Your CDMO Selection Process

The number of biologics in development continue to increase at a rate and contract development and manufacturing organizations (CDMOs) are responding to this rapid rise in business. With this growing market breeding new competition each year, the CDMO outsourcing options available to drug sponsors can be overwhelming. Finding the CDMO that is right for your company and project can be a daunting task, particularly if this is your first time outsourcing. Some companies, especially those with limited experience in the biopharmaceutical industry, may find themselves unprepared when it comes to beginning the search.

Without careful consideration of what are the most important features you need from a CDMO and preparing for what the CDMO needs from you, the result can be a mismatch between the CDMO's core competencies and the sponsor's expectations. In the case of technology transfer of an R&D or GMP manufacturing process, if insufficient information is provided on the processes required for manufacturing or the anticipated scale, the CDMO will have difficulty assessing the scope of the project. This can ultimately affect their ability to give accurate timelines and contract information. When the sponsor gathers specific information before contacting the CDMO, it allows for a more productive and accurate technical discussion between the CDMO and sponsor and increases the success rate of the program.

Here are five questions you should be prepared to speak to in advance of contacting a potential CDMO:

1. HOW MUCH MATERIAL WILL YOU NEED FOR YOUR PROJECT?

The CDMO you select must have the capacity to produce the amount of product you need and will ask questions based on that need; therefore, you should determine your best estimate of the amount beforehand. This requires knowledge about:

- the number of patients in your clinical trial the dosing regimen
- the amount of drug substance and drug product required for lot release and stability testing
- the overall yield of your process
- the size and type of vessel needed, i.e., a fermenter or a bioreactor
- the size and type of downstream process equipment needed, e.g., chromatography column volume or tangential flow filtration capacity

With this knowledge in hand, the CDMO can then accurately scope the project and potential start date, based on whether they have the capabilities available for your project's specific needs.

2. WHAT IS YOUR TIMELINE?

Along with scale, the CDMO will want to know your target dates for starting the project and when you need to have the final product. Often, sponsors taking their first drug from a pre-clinical to the clinical trial stage may not have a full understanding of all the factors required for cGMP manufacturing and release of final product for clinical trial. Feedback from the CDMO and an explanation of the steps required for the project scope of work will be useful for the drug sponsor to assess if the proposed timeline is achievable. Some program aspects that may not be initially apparent, but are critical to the timeline for releasing final drug product, include:

- drafting, review, approval, and issuing of batch records and raw material and product specifications.
- cleaning, inspection, and release of manufacturing suites and equipment by quality assurance (QA).

- safety and identity testing of cell lines prior to use by the CDMO.
- generation, testing, and release of master and/or working cell banks prior to use in manufacturing.
- in-process control testing for process decision-making executed batch record review and resolution of process deviations.
- final product release testing.

3.HOW SCALABLE IS YOUR CURRENT PROCESS, AND IS IT READY FOR MANUFACTURING?

Culture processing, product extraction and clarification, purification, and formulation strategies that are developed at the R&D level may not be scalable or suitable for manufacturing scale production. For example, this can include cell lysis with detergent, buffer exchange using dialysis, some types of affinity chromatography, and size exclusion chromatography. Processes for buffer exchange steps, concentration, and final formulation requiring the use of tangential flow filtration (TFF) at the manufacturing scale may not have been optimized since they are often not used for scale process development. Other factors, including temperature control of in-process steps, also need to be considered, as the large scale manufacturing processes may only be feasible at ambient temperature. Hold steps and product stability are also important factors when assessing the overall manufacturing process and the readiness for manufacturing.

It is important to consider if the process is robust enough to be performed without further process development or process optimization:

- Are the yields sufficient enough that cell culture or fermentation conditions do not require further optimization?
- Do the current chromatography steps remove contaminants necessary to meet drug product release specifications?
- Are all processes scalable?

In general, if you plan to tech transfer your process directly from R&D, you will need to allot time for the CDMO to complete process development and optimization to prepare it for larger scale GMP manufacturing. This can take a few to many months, depending on:

- the number of process steps that require optimization
- if new process steps are required to achieve suitable purified product quality and purity
- if knowledge exists about in-process product stability and hold steps

If the product has not been previously manufactured and a CDMO is selected that does not have a process development group, the sponsor may incur considerable risk. If something unexpected occurs with the biological product during scale-up, the CDMO may not have the capabilities to investigate and correct the issue.

4. ARE THE ANALYTICAL METHODS FOR IN-PROCESS TESTING AND FINAL PRODUCT RELEASE ADEQUATELY DEVELOPED?

If special analytical methods are required for in-process testing and final release of the product at the CDMO, these methods will also require technology transfer. It is important to communicate any special equipment requirements to the CDMO and have a clear understanding of what analytical expertise is required. Specifically, analytical assays should have the required sensitivity and reproducibility for the intended purpose. If the quantitative results need to meet certain specifications, then assay qualification or validation will be required in a clinical-stage appropriate manner.

On the other hand, the assay may be "for information only" (FIO) and /or give qualitative results that might, for instance, be used in determining which fractions eluted from a chromatography column contain the desired product. If this is the case, then technology transfer of the assay protocol for drafting a customer-specific SOP may be sufficient. If the analytical methods do not meet these qualifications, analytical development may be required.

One needs to decide if analytical development will be performed by the CMO or by the sponsor's analytical team. If the results from analytical tests for in-process testing are gating and results meeting specific criteria are required prior to proceeding with the next unit operation, it should be considered how this will affect critical hold times and if there are less technical analytical tests that can be substituted. For example, high-performance liquid chromatography (HPLC) may have been used at the R&D and pilot stages of process development, but spectrophotometer absorbance readings might be adequate and faster at the GMP scale.

5. HOW MANY PARTNERS ARE YOU WILLING TO WORK WITH?

The best answer to this question would be only one in order to avoid communication or timeline management hiccups but that is not always practical. Adding multiple partners to a project means managing timelines between each company and ensuring clear and consistent communication from beginning to end. Both of these tasks can be very challenging in a multi-partner structure. To minimize using multiple partners for your project, ensure the CDMO you select has many or all of the competencies necessary, such as cell banking; process development; formulation; and analytical method development, qualification and release testing, in addition to GMP drug substance and drug product manufacturing capabilities.

It is also important to consider scale-up needs based on projected additional clinical trials. You should be prepared to discuss the projected scale-up timeline with the CDMO. Based on their capabilities, they might be the appropriate CDMO only for early stage but not late stage clinical trials.

Switching CDMOs at multiple stages of clinical testing may increase costs and the time to commercialization. However, CDMOs specializing in early stage clinical trials may be the best fit because of flexibility and nimbleness required to quickly enter the clinical for Phase I. If there are important deadlines, such as filing and Investigational New Drug (IND) application or start of a clinical trial, sharing this information with the CDMO allows them to assess if they will be able to realistically meet those deadlines.

Gathering these answers can prepare you for the questions a CDMO will ask as well as generate more questions that you will want to discuss during your selection process. You should provide the candidate CDMOs with as much information as possible so they can evaluate if the production process is well-suited to their existing facilities and expertise or if it is outside of their capabilities. Ask the necessary questions in your first conversation so you understand early in the selection process the limitations and advantages of each CDMO you interview.

Step one will be a general inquiry to the CDMO to determine if they have the capabilities to execute your product's manufacturing process. If there is a potential fit, then a confidentiality agreement will need to be developed and agreed on before the sponsor and the CDMO can discuss the process and any development needs in detail. Prior to scheduling a technical call, you will want to send a packet of information describing the product, the processes used in production, and the scale and timeline of production that you anticipate. Typically, the CDMO's Business Development group forwards this information to the technical staff and scientists. Expect to allow at least a week for review so they can accurately assess the scope of the project and

prepare requests for additional information. During your initial discussions, the CDMO will likely present you with an overview of their capabilities. Some basic information you will want to gather is whether size of the fermenters or bioreactors available meets your needs and if there is equipment available for cell harvest, protein or plasmid extraction, chromatography equipment, and aseptic vial or syringe fill-finish.

Here are five questions you should ask your potential CDMO partner during your initial conversation:

1. WHAT QUALITY SYSTEMS DOES THE CDMO HAVE IN PLACE?

A CDMO with an appropriate on-site quality assurance (QA) group should have a manual the outlines their quality strategy and should be able to demonstrate they are able to handle any necessary investigations and/or resolve any deviations. If the CDMO is outsourcing or contracting QA, it may take longer to release the product.

2. HOW IS TROUBLESHOOTING HANDLED DURING SCALE-UP?

For CDMOs with a formal process development and/or technology transfer group, troubleshooting activities can be completed on-site. If the CDMO does not have a process development or technology transfer group, the alternative is for them to take as issues back to the client to handle themselves. They many also simply proceed at risk to the customer with the potential of a failed production run. Either way, it is important to know how issues with your product will be handled.

3. CAN ANALYTICAL TESTING BE DONE ON-SITE?

CDMOs may outsource all or some analytical testing to a third party, such as sterility, bioburden, and endotoxin, so it is essential to understand how in-house and outsourced testing strategies affect the release timeline for a product. It is also important to know if analytical development is available on-site should these methods need to be developed or optimized.

The advantage of having analytical development at a CDMO is that the technology transfer to their QC group will likely be a smooth transition, rather than transferring it from either another company or from your company directly. An analytical development group at the CDMO can also quickly provide troubleshooting services when they are needed.

4. DOES THE CDMO ALLOW PEOPLE IN PLANT (PIP)?

The ability to monitor a process while it is in production is something that varies among CDMOs, so you will want to ask if they allow a representative from your company on-site during production. For example, CDMO offers suites equipped with cameras for sponsors to monitor the process. This provides the sponsor with the ability to monitor the operations in real time and to provide feedback.

5. WHAT IS THE CDMO'S PROJECT MANAGEMENT AND COMMUNICATION STYLE?

The ability to communicate effectively throughout the project will have a major influence on the overall outcome. The communication style and culture of the CDMO selected must align with the sponsor's in order to ensure a productive and profitable working relationship. The CDMO may have a project management group that assigns a project manager to your project. The drug sponsor should ask the CDMO to describe a typical project management scenario. The CDMO may be flexible regarding the frequency and method of contact (e.g., email, phone, teleconference, on-site visits). If so, you should be ready to indicate how you would like information exchange to take place.

Finally, for those CDMOs being seriously considered, it is recommended you make a short (two- to four-hour) follow-up visit to tour their facilities. This allows you to perform due diligence and feel confident about the

people and the organization. Be prepared to present a flow diagram of your process and discuss any critical points in the process as you will likely meet with a larger group of employees than you've spoken to previously. This gives members of the technical groups at the CDMO a chance to further evaluate the readiness of the process for manufacturing at their facility or if they require additional process development. They may also reveal at that point a limitation in their experience or expertise that are critical to your process that weren't recognized initially.

Picking the wrong CDMO partner can have detrimental effects to the timeline, costs of a project, and overall success of a program, which can be especially harmful to a small pharma company with limited time, resources, and budget. By practicing due diligence during your CDMO search, you can ensure the selection of a partner whose business strategy not only aligns with yours but also provides a pathway for long-term success and stability. You will know you picked the right CDMO partner when you observe that the members of the CDMO team care as much about your product as you do.

Reference: Preparing For Your CDMO Selection Process (pharmaceuticalonline.com)