ARTICLE

How to pick the right CDMO for late-phase clinical trials

Asking the right questions to optimize a critical decision on the pathway to commercialization

For pharmaceutical companies without their own facilities, choosing the right partner for late-phase clinical trials and commercial production is a critical consideration in developing parenteral products. Small contract development and manufacturing organizations (CDMOs) can often provide early-phase material but may not always be able to move through to meet the rigorous demands of late stage and into commercialization. This article examines some of the key criteria for selecting the right CDMO partner and includes a case study that shares some challenges involved in a late-phase technology transfer for a parenteral product.

Perspective on Phase III

A great deal of work must be done on a product over the course of several years by the time it reaches Phase III clinical trials (*see Figure 1*). While the design of Phase III trials can vary widely depending on factors such as the type of therapy, the patient population and the study design, there are some broad similarities (*see Figure 2*). In general, Phase III work can last 1–4 years and can include as few as 300 patients and as many as 3,000 patients. Once a product has reached Phase III, its chances of eventual commercialization are high, with FDA figures indicating a success rate of 58–60%. This compares with around 25–30% of molecules entering Phase I actually reaching Phase III and gives some indication of the level of importance attached to ensuring the effectiveness of this critical stage.

Typical costs of Phase III development and clinical trials for a biologic are high. The CDMO portion accounts for only about one-quarter of the total cost, but at this stage, the ability to manufacture robust and stable drug substance and high-quality drug product is crucial to the trials' success. With the work ahead including all the process characterization, process validation, final scale-up and the identification of critical process parameters, it is essential that any partner organization has the capability to push this through, meet the timelines and support regulatory submission for a timely and successful product launch.

Trends in partner selection

A recent *Pharmaceutical Technology* survey of pharmaceutical industry professionals asked if they would consider switching CDMOs when planning for Phase IIB/III clinical trials and also why (*Figure 3*). For drug substance development, 60% said yes; for drug product development, 45% also said yes (*see Figure 3*). Scale and capacity were factors in those decisions, as were price and timeline, with some citing the need to improve relationships and quality. Key trends were:

- Capability match, flexibility and options
- Technical expertise
- Ability to meet timelines
- Global presence
- Cost

Companies often change vendors at this stage because they need to move from a small CDMO that perhaps could support the clinical phase to a larger company capable of going right through to commercial production. Scale and capacity are important, and it may be that a smaller organization lacks the equipment to generate the batch sizes required or has lines of insufficient scale to achieve the speed necessary for large batch production. Similarly, a product's format or delivery method may change as it moves into Phase III. A switch from vials to pre-filled syringes is a prime example, requiring a move to a CDMO with the relevant expertise. Experience in areas such as process validation and commercial launch must be considered, and there is frequently a desire to reduce the number of vendors and simplify vendor management as development progresses.

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Figure 1: Defining Phase III clinical trials

Figure 2: Phase III perspective

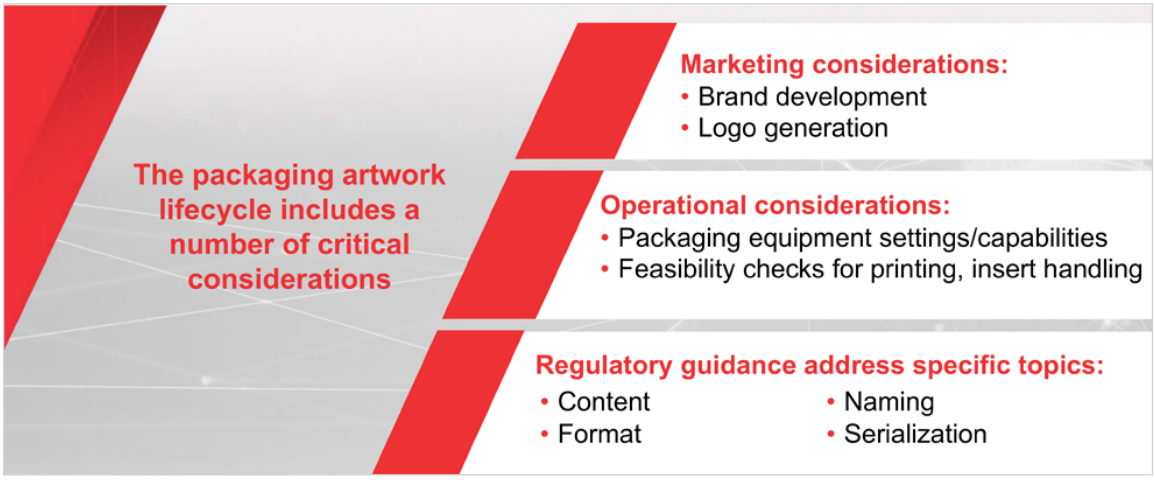

Figure 3: Pharmaceutical Technology survey results: considerations for switching CDMOs in late-phase development of drug products and drug substances.

Criteria to consider

One way of approaching the process of evaluating a CDMO is to consider three categories of capability. First is regulatory, quality and supply chain. This includes factors such as regulatory support, redundancy in the network, global footprint and quality oversight. Second is technical, which encompasses both experience and facilities. Third is organizational, understanding how a CDMO works with its clients and whether it views them as critical partners. Some key topics within these categories are explored in more detail below.

Regulatory support and track record

It is important to consider the CDMO's site and track record and be mindful of the level of regulatory support actually required. Understanding how often a site is inspected, by which regulatory bodies and whether or not this aligns with the intended markets for the commercial product has a bearing on whether a candidate CDMO is a good match. Diversity in the agencies inspecting the site is helpful and companies should be able to provide their inspection histories. Finding out if the company has any Form 483s issued by FDA inspectors and how they are being addressed is also indicative of performance, as is knowing whether any pre-approval inspections (PAIs) have been waived recently. This all helps build confidence that the CDMO has experience with relevant approval processes and is inspected by a range of different agencies.

In terms of matching this experience to the regulatory needs of a prospective client that does not have the luxury of an in-house regulatory department, there are also questions of which types of product the CDMO has been involved with, large or small molecule, for instance, and which scale. Moreover, is an on-site team dedicated to regulatory support and can they provide all the required information to support regulatory filings?

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Scale and options

Scale and available production options are major considerations for many pharma companies when a product is approaching Phase III. Capabilities are reflected in a CDMO's facilities and approach, and several areas must be probed.

Does the CDMO have the ability to scale up? Determining any batch size limitations and finding out exactly how a product and process would be scaled up is essential. The CDMO should ideally present options for increases in scale and demonstrate that they have the capacity to meet commercial demand. It is especially important to look at projections for the first three to five years of commercial production and assess whether it could be met.

Is the site flexible and able to make any adjustments required for a specific product? Scaling up will most often mean using different equipment and if the CDMO doesn't already have something in place, it is necessary to know if it has the ability to adapt and change that. As more biologics go into production, for example, a CDMO is more likely to need large fillers that have low-shear peristaltic pumps for delivery of these products.

Does the CDMO have built-in redundancy, should a second source be needed? Assuming sales growth of the commercial product or the desire to distribute in different geographical areas, then the option to manufacture at more than one site is attractive.

Defining a technical match

Capacity, scale, timeline and costs are all important, but a technical match is critical to success. Considering whether the CDMO offers the services necessary for the complete scope of the project means finding out what is available and if something is not currently on offer, if this can be changed. A simple example might be working with a different vial size or syringe type, and the ability to adapt equipment to accommodate these.

An effective CDMO understands the challenges of working with particular types of product and from a client perspective when evaluating a partner organization, this means exploring their history. Questions might focus around the types of molecules they have worked on, how much of that work has been on small versus large molecules, number of lyophilized versus liquid products, and so on. The organization should be capable of both comprehending and mitigating any risk.

Technology transfers raise many questions and there must be clarity to the process. A CDMO should demonstrate that they are well versed in completing the entire package around tech transfers, including all the analytical, quality and validation aspects that are critical at late phase and into commercial production. Since early-stage production processes are not necessarily the most elegant, it may also be expected that a CDMO will proactively look to improve process design as a project moves into the late stages, in order to ensure a high-quality commercial product.

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Finally, the analytical services must match requirements. While third-party testing is always an option, there is much to be gained from performing both incoming identification and final release testing at the same facility, especially where there is a goal to simplify vendor management.

Relationships and culture

Many different teams are involved in Phase III studies, moving a product through process characterization, process validation and into commercialization. A CDMO should be able to demonstrate that it has the relevant groups in place, that they work well together and have a successful track record of pulling products through from late phase into commercial production. Learning how the project team will work both internally and externally and understanding the lines of communication sets the stage for a successful venture. It is important to know who manages the project and the communication, as well as the level of involvement of the organization's management team and any escalation processes. Whether or not the site has a process improvement team and continuous improvement goals can be a good indicator of an organization's culture. How it regards its clients is of paramount importance and thinking as partners rather than customer and service provider bodes well for success. In addition, the CDMO must understand that the needs of small and large pharma companies differ and can be accommodated.

Technology transfer case study

Having identified a successful technology transfer as critical to a project's outcome, the following case study provides a useful illustration of some challenges that may be faced and the technical knowledge and expertise that must be applied to find and implement effective solutions. It describes the technology transfer and production scale-up of a delicate antibiotic product moving between facilities within the Thermo Fisher Scientific group.

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Clinical batches of an antibiotic product were produced successfully at a European site for early-phase work and moving into late phase. This site did not, however, have the capacity to scale up, and the client intended to launch first in the US followed by Europe. The process was therefore moved to another facility within the network and because of the launch market, a US site was chosen.

While the process parameters were well defined, multiple technical challenges were associated with this product's manufacture (*see Figure 4*). The API was both oxygen and moisture sensitive, and the solution was sensitive to stainless steel and heat. Therefore, many controls were in place to meet the requirements of working within these constraints.

Scaling from small to large scale also created issues with hold times and those detailed in Figure 4 were critical. While the six hours from API addition to completion of the pH adjustment does not appear difficult, in practice the pH adjustment had to be performed very slowly because of localized high pH, necessitating the creation of a process to manage this work within the specified time frame. The API also took a long time to dissolve and required slow addition, therefore the six hours started as soon as that addition began.

The most critical time was the 20 hours from API addition to initiation of lyophilization and included not only the 6 hours from API addition to pH adjustment but also an in-process HPLC which took around 6 hours to run, followed by final quality checks, filling and then freeze drying. Twenty hours was not difficult to achieve for the smaller batches but proved very challenging at a larger scale. Further, the filling line had a hold time of 30 hours after sterilization in place (SIP) to the end of the filling.

Figure 4: Technology transfer case study: Product A

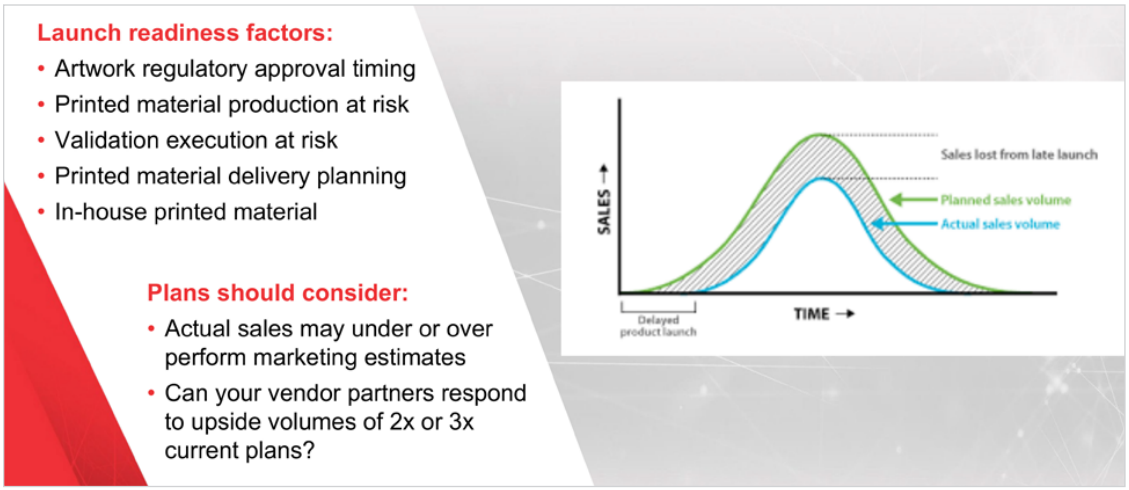

Figure 5: Managing tech transfers and mitigating risk.

Several processes had to be put in place to further address the sensitivities of the API and the solution. These included applying nitrogen sparging and using disposables to avoid stainless steel contact, implementing dissolved oxygen measurements and using a jacketed tank for active cooling.

Many risks were associated with the project, which started at late phase and moved through to registration and finally to validation. Figure 5 shows some of the details and how the challenges were addressed in taking the process from 15,000 to 48,000 vials. Key to the whole process was the design of a customized disposable bag for use in the jacketed tank in order to implement sparging in a disposable. This had not been done before without some stainless-steel components. Improving upon the hold time was also crucial as the 20 hours was too high of a risk for commercial manufacturing. Study and development of the process resulted in an extension of the hold time to 26 hours. Raised stopper detection, not previously available in the facility, was installed to meet the needs of the scaled-up process and a full failure modes and effects analysis (FMEA) was performed with mitigation steps put in place for all identified risks (*see Figure 5*).

This successful project resulted in the completion of three registration batches. Process improvements were made, and a robust process designed and executed prior to process validation batch production. Commercial launch of the product is imminent and a second site in Europe is taking all the learning from the US, making the technology transfer process much easier.

Fundamental to the success of the project was the communication between operations and QC laboratories, having the customer onsite during production to expedite decision making, and recording very specific batch instructions and ensuring advanced operator training for these highly technical batches.

Summary

Selecting the right CDMO partner for late-phase work is fundamental to successful commercialization. Significant areas for evaluation are technical fit, alignment with regulatory expectations and adequate support systems. On the technical side, a partner should adopt a scientific and risk-based approach, be flexible and accommodate technical challenges. Where regulatory requirements are concerned, experience with a variety of agencies is helpful as is expertise in working with relevant molecules. Good support throughout is essential. A partner must be able to provide this for all aspects of a program and have a clear process for technology transfers. Critical evaluation and fulfilment of these criteria is essential to achieve a smooth and successful technology transfer program.

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