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Mind the Gap: Tech Transfer from Early Stage Cell Culture to Phase I Clinical Manufacture

Tech transfer is key to succession advancing pipeline products from research to preclinical.

Feb 01, 2019

By Barrett Fallentine [1]

Pharmaceutical Technology
Volume 2019 Supplement, Issue 1, pg s6–s9

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In 21st-century biopharma, no longer is "bigger" viewed as "better." Many small pharma and biotech companies operate with leaner, often virtual company structures; tight budgets and timelines; and results-oriented cultures. Consequently, to advance pipeline products from research to preclinical, partnering with contract development and manufacturing organizations (CDMOs) is necessary, and assembling a robust technology transfer package is key to success. This article shares some best practices for technology transfer based on lessons learned in transferring an early-stage cell culture process to a CDMO for Phase I clinical manufacture.

During the lifecycle of a typical manufacturing process, there will come a point where it must undergo a technology transfer. In the case of large pharma, this often occurs internally from the development team transferring a lab-scale process to the manufacturing team to scale it up. For smaller companies that lack a good manufacturing practice (GMP) infrastructure to produce their drug products for clinical studies, they must transfer their process to a CDMO to produce material to fuel preclinical and Phase I studies. **Figure 1** shows a typical tech transfer process flow. Depending on experience, each company uses its own technology transfer methodology, comprised of internal expertise and proven rules-of-thumb.

Figure 1. A typical tech-transfer process flow; PD is process design.. Figure is courtesy of the author.

CDMO: choose the right fit

During early drug development, successful selection of a CDMO can be difficult for a number of reasons. Manufacturing schedules are often set years in advance, costs can be high and, depending on how established a CDMO is in the industry, the level of experience and expertise can vary. Smaller companies are often under a tight timeline with a limited budget. So, when choosing a CDMO partner, it is important that they have experience working with smaller companies and have a solid technical team that is accustomed to rapid decision-making, with the ability to solve the types of technical problems that occur during development and manufacture.

Assemble the team with communication in mind

Successful technology transfer depends on reliable communication, planning, and documentation executed by results-oriented team players, which involves assembling appropriate members from both sites (sponsor and CDMO), ideally with each member having a counterpart to ensure direct transfer of knowledge and good communication. Depending on the CDMO, there may be separate teams for manufacturing and process development. Be sure that both groups have representation because when problems arise, the two groups must communicate well with each other so that the flow of information continues.

As an example, in one case a sponsor called the his CDMO counterpart in the middle of the night to say that an operator had added the wrong amount of feed medium to a production run. It turned out that the scale had been incorrectly calibrated and was measuring in pounds instead of kilograms. Fortunately, this error was caught early enough to fix it by performing a quick calculation and adding the remaining amount. It was also fortunate that the sponsor knew he could call his CDMO at any time. The lesson is: be sure the technical team is able to ask their counterparts questions to assess compatibility and gauge experience with similar products. Find out how they troubleshoot when problems arise. Make sure they have a scale-down model. Ask to view some blinded data from a previous tech transfer or scale-up. In this type of endeavor, a picture is worth 1000 words.

Process knowledge and documentation: completeness is vital

Assembling a robust and complete documentation package is crucial to the success of any tech transfer. A well-developed tech package will enable a project to be transferred with a minimum of setbacks. Sometimes small companies try to capture everything in their technology transfer documentation for early-phase tech transfers. They will often have stability data, a complete set of analytical methods, and complete product specifications. And there is nothing wrong with having all of that because it will be useful for later phases (Phase II/III) in a product's lifecycle, even if it isn't necessary for early drug development. Keep this in mind, as it can save time. A typical early-phase technology transfer package includes at minimum the following documents:

Product characterization data: The sponsor must provide a quality target product profile that includes critical quality attributes (CQAs), release specifications, and any preliminary stability information.
Process description: It is the responsibility of the sponsor to provide a detailed description of the final process they would like to transfer. The process description should contain all process parameters and conditions and CQAs, and it should be as detailed as possible. It should also include any lab or small-scale batch records as well as a discussion on any critical operating parameters.
Process development and cell line development reports: The process development site must document why certain decisions were taken and why certain parameters or conditions were selected while others were not during process development. Availability of this document to the CDMO allows understanding of critical process parameters and enables decisions about how to execute each process step with acceptable margin of all parameters and conditions. If at all possible, it should include a scale-up rationale and any pilot batches conducted.
A brief description of analytical procedures with proposed specifications and acceptance criteria: Keeping in mind that this stage is early drug development, it is not expected that all methods and specifications be defined for a Phase I biologic. For a Phase I biologic, analytical methods should be in place; however at this early stage, they do not need to be validated.

There is an expectation that throughout the development lifecycle, the manufacturing process will evolve and improve with gained knowledge from more production batches, which also holds true for the analytical methods associated with the product. Often small companies do not have this in mind and invest more time than is merited based on the phase of their product. Extensive process and product characterization becomes more important for Phase II and Phase III products.

Identifying risks and facility fit

After completing document and knowledge transfer, the CDMO will typically perform a facility fit assessment to discern any additional gaps and risks. This exercise involves a step-by-step analysis of how the entire manufacturing process would be performed at the CDMO with the goal of identifying any potential process, facility, or procedure changes needed to fit the process into the CDMO's facility. The output of the facility fit analysis should be a comprehensive list of possible gaps and should be jointly developed by both the sponsor and the CDMO. Typically, formal summaries and process flows are provided, including suggestions on how to adapt the process to the CDMO's facility and equipment as well as an experimental plan to test potential new procedures at small scale. Once the knowledge/documents have been transferred by the sponsor to the satisfaction of the CDMO, the identified activities required to confirm the transfer are completed, including closing gaps and reducing risks.

Demonstration batches are a must, ideally at-scale

Take the time to do a demonstration batch that incorporates all of the process design batches that were conducted to address facility fit gap. One item most worth spending the money on is an at-scale engineering batch. An at-scale engineering batch may appear to be costly, but it saves time for subsequent batches. It allows for extra in-process sampling, refinement of manufacturing batch records, and related GMP documentation, adjustments to the process as required by facility and equipment differences, and a reduction in the cost of the initial, high-risk, full-scale production. By running at least one such batch at scale and adjusting some parameters based on the data from that run, a company can reduce the risk of its initial GMP batches failing.

No transfer is without hiccups

No technology transfer is perfect. It is inevitable that issues and problems arise. The best advice is to keep communicating. When there are oddities in a batch, people may get defensive—particularly if the batch does not meet specifications, or if there were anomalies along the way that were not reported to the sponsor. Identifying a CDMO that is of a similar mindset, has good communication, and is accountable when issues come up is key.

Article Details

Pharmaceutical Technology
Supplement: Partnering for Bio/Pharma Success
February 2019
Pages: s6–s9

Citation

When referring to this article, please cite it as B. Fallentine, "Mind the Gap: Tech Transfer from Early Stage Cell Culture to Phase I Clinical Manufacture," Pharmaceutical Technology Partnering for Bio/Pharma Success Supplement (February 2019).

About the Author

Barrett Fallentine is director of Product and Process Development, Pharmatech Associates, bfallentine@pai-qbd.com [2].

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