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How to Ensure Smooth Technology Transfer

A comprehensive process and analytical transfer package can speed up your product's time to market and save costs

At some time in a biopharmaceutical product's journey to market, the process by which it is manufactured must be transferred from one site to another. The reasons for the transfer can vary depending on the type and size of the company. But no matter where the process goes or why, one thing is certain. Unless the donor and receiver sites have effective and comprehensive technology transfer capabilities in place, the move will be subject every step of the way to Murphy's Law: whatever can go wrong, will go wrong.

Lack of documentation, lack of appropriate personnel involved in the transfer, or shortcuts like forgoing mutual site visits by donor and receiver personnel can result in the recipient being unable to replicate the process or efficiently correct it when it goes awry. As a result, time to market grows longer and additional costs pile up. And for new companies dependent on funding at each development milestone, missed timelines can be deadly.

Even in organizations with years of experience in cGMP manufacturing, technology transfer is often plagued by multiple problems. In a recent survey, we found that technology transfer is far from a core competency in the industry today. Budget and schedule overruns occur far too often. Most companies do not use dedicated teams to execute tech transfer. Moreover, the transfer of process knowledge is often ineffective.

For companies that have never transferred a process, the challenge may seem especially daunting. It doesn't have to be. By making the process and analytical transfer package (P&A-TP) the focal point

By making P&A-TP the focal point of the effort, you can accomplish the technology transfer rapidly.

of the effort, you can balance the goal of accomplishing the transfer rapidly with the goal of making as few mistakes as possible. A comprehensive P&A-TP coupled with carefully designed technical transfer protocols (TP) derived from it, can enable a smooth technology transfer of your process.

DIFFERING TRANSFERS

Technology transfers of course differ in their circumstances, their stringency, and their purposes. For example, the transfer may take place from one site to another within your company, or from your company to an external site like a contract manufacturing organization, or a company that has licensed your product. In both cases, the move could be across borders. Because the creation of the P&A-TP and the protocols requires close cooperation between donor and recipient, an internal transfer would appear to be easier. Large companies, of course, already have a standard internal P&A-TP process in place. But for many early-stage biotechs, no such framework exists. And in creating one, they should be on guard against being lulled into complacency by the fact that the transfer is internal.



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A transfer outside the company may require more persistence in securing fully comprehensive information from the external partner. Moreover, because the transfer is external, your organization may inadvertently withhold critical information out of concern for your intellectual property. When the transfer occurs across borders and cultures, such difficulties and concerns may be compounded.

Technology transfers may differ in other ways as well. For example, during Phase 1 or Phase 2 development, the transfer may be undertaken to determine whether the product can be successfully manufactured from a laboratory-scale process to a pilot scale producing cGMP material for the first time. Such an early-stage transfer is relatively less demanding and time-consuming than a transfer in Phase 3 for full-scale cGMP production and commercialization, with far more stringent requirements for compliance and process validation. In either case, however, a comprehensive P&A-TP can make all the difference between an efficient transfer and a process bogged down in rework, inadequate protocols, and repeated calls from the recipient for more information.

Depending on the circumstances, the specific responsibilities involved in creating the P&A-TP and the protocols may be divided in a number of ways. Generally, however, when there is no pre-existing P&A-TP, both the donor and the recipient collaborate closely on creating one. For example, the donor may create a preliminary P&A-TP based on the equipment, scale, and other operating conditions of the process at its site. The recipient may then edit the donor's preliminary P&A-TP based on conditions at the recipient site and return the document to the donor, along with requests for additional information, if needed. Once both parties have agreed on the final P&A-TP, the transfer protocols are created either

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by the donor or the recipient—again, depending on the particular circumstances of the transfer.

COMPONENTS OF THE PACKAGE

The P&A-TP should define a process as it is to take place under GMP conditions at the scale desired. Written from pre-GMP batch records and other documentation, it should fully describe process parameters. Further, it should be updated throughout the process of the transfer until successful GMP manufacturing is achieved and, in the case of transfers for commercialization, the process is validated.

Regardless of which party writes the final P&A-TP, or whether both parties create it together, the P&A-TP should include the following components:

Process Description: Based on molecule and process knowledge accumulated during research and development, this description includes the sequence of operations for the process, the rationale for each process unit operation, initial operating ranges for process parameters, in-process controls, and initial acceptance criteria for the product. As the receiver conducts experiments and manufactures test batches, the description will be revised to characterize the process in light of new knowledge. Companies often generate a schematic representation of the process, generally referred to as a process flow diagram, that provides a snapshot of how the process will be executed during manufacturing.

Equipment List: This includes details of the equipment that will be used at the receiver site to manufacture the product. Such a list is

always important, but it is even more important if the receiver's equipment differs from that of the donor and if scale-up is desired. Changes in the equipment can be addressed during the execution of transfer protocols to ensure that product quality is not affected by equipment change.

Bill of Materials (BOM): The BOM typically lists all raw materials and process consumables that will be used to manufacture the product. This helps in identifying key attributes such as long lead-times for procuring the materials and consumables, amounts that are needed for the specific manufacturing campaign, and special tests, if any, that need to be performed for acceptance.

Analytical Package: The analytical transfer is a separate exercise that occurs either in parallel or before the process being transferred. The state of analytical method development at the donor site can severely impact the transfer and successful execution at the receiving site. Typically, in early development, release assays (used to monitor product safety, identity, strength, purity, and quality); stability-indicating assays are qualified and subsequently validated at a later stage (before process validation). Although it is important to ensure that assays for release and stability are appropriately qualified, you should also make sure that in-process assays (especially those that monitor titer) are appropriately developed and qualified.

Along with the process and analytical transfer package, it is essential to have a list of samples that will be pulled at different process steps to be tested (for in-process,

release, characterization, and stability), or stored as retains to support potential investigations. As this list is compiled, it often turns out that the final amount of product available for preclinical or clinical use may be much less than had been anticipated.

The P&A-TP should also be accompanied by other relevant documentation from the donor. This list should include development batch records, process and analytical development reports, assay qualification reports, and test methods. Guidance from the donor on process ranges and operating parameters as well as initial specifications are very helpful in compiling the development of transfer protocols and batch records at the receiving site. Any information that is inadvertently not included in the initial documentation may be obtained by interviewing the appropriate personnel at the donor site, documenting the interviews, and adding appropriate information to the transfer documentation. Further, throughout the transfer process, both sides should not only communicate fully and often, but also meet face to face. The personnel from the receiving site should become process experts by visiting the donor site and, conversely, donor personnel should be present for initial runs at the recipient site.

The analytical protocols ensure that the relevant analytical attributes are evaluated and met during and after the manufacturing of the product.

THE TRANSFER PROTOCOLS

With the P&A-TP in hand, the technical transfer protocols (TP), designed to guide the implementation of process as it is to be performed, can be created either by the donor, the receiver, or both. The TP includes protocols for the process to be transferred and protocols for the analytical methods to be transferred. The process protocols describe the acceptable operating limits of the process and equipment that, if achieved, enable the product to meet its specified quality characteristics. The analytical protocols ensure that the relevant analytical attributes are evaluated and met during and after the manufacturing of the product.

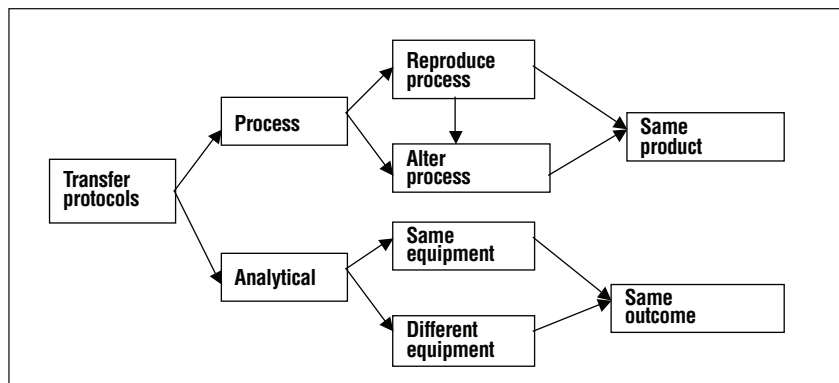
Typically, the experiments conducted during transfer runs, especially for process transfer, are performed in the process development laboratories of the receiving site at a reduced scale, taking into

consideration the factors critical for the scale-up of the process. This approach is common when transferring processes for the manufacture of Phase 1 or 2 material. However, for processes that are being transferred to generate Phase 3 and commercial material, the transfer runs are typically carried out at-scale, with resulting process and analytical data being included in appropriate comparability reports.

If, as sometimes happens in large companies, identical equipment is in place at both the donor and receiver sites and there is no question of scale-up, the process and analytical protocols will remain fundamentally unchanged, as Figure 1 depicts. If, however, scale-up or commercialization is the goal, or the equipment at the two sites differs, the process protocols and the analytical protocols must be altered to ensure that the process yields the same product and the analytics yield the same outcomes as occurred at the donor site, as Figure 1 also shows. Further, it sometimes happens that the donor believes that the process can be reproduced at the receiver site, but the receiver is unable to do so. In that case, the process must also be altered.

In creating the process and analytical transfer package and deriving carefully designed technical transfer protocols from it, you move with all deliberate speed toward your goal—the acceptance of the process at the receiver site and, ultimately, the market. ♦

Figure 1. Transfer protocol pathways





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