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WHITEPAPER

Technology transfers: reaping rewards, reducing risks

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Abstract

Technology transfers between sites can pose risks but can also offer significant rewards. Often times, challenges include logistics, differing equipment and processes, and staffing issues at the receiving facility. Decision makers look at the risks: potential low yields and the rejection of product resulting in the inability to deliver the medications to patients and financial loss.

A comprehensive risk assessment is vital and a plan to address them in a timely manner will provide safeguards. Staffing should top the list of critical concerns with a focus on building trust between the senders and receivers, and appropriate investments need to be carefully considered. Rewards can can come in the form of product improvement, increased production, and monetary gain. A well-planned transfer of production can far outweigh the risks.

Introduction

There are a number of strategic advantages companies can achieve in pharmaceutical production by transferring production between sites. They can safeguard supply by producing at more than one site, and improve distribution by moving production closer to critical markets. They can also reduce program costs and risks by moving production to sites that are better qualified, able to produce more economically, or are better positioned to meet the needs of regulators.

For several reasons, transferring production—and the technologies that undergird it—can be risky. The same product can behave differently with various equipment, resulting in low yields or even batch rejections. Staff at a receiving facility may not have the proper technical skills to execute a specific process; or there simply may not be enough trained staff on site to ensure the job is done correctly. Also, even as companies may not take the time—or expend the effort—to create and provide good documentation of their product or process, their partners may not invest the necessary resources to ensure efficiency and quality.

If any of these occur, you could suffer the loss of time and money in remediation, and patients may not receive important medications. The net of these risks is that companies do not transfer production as often as they probably should.

However, Thermo Fisher Scientific has extensive experience in technology transfers and has developed processes and techniques for reaping its rewards while reducing its risks.

When it works: Three successful transfers

1

Product X

The product was a registered intermediate of a novel first-in-class API being produced for a client in a 10-step process. One high-temperature step was especially complex, requiring good control to balance quality and yield. We were spending a disproportionate amount of time and effort getting this step right, and we knew that other manufacturers—with more experience in this specific technology—could likely do it better. Accordingly, we set out to find a manufacturer who could take over this production step for us, and we found one in China that could supply our plant in Austria. To get the process up and running on the supplier site in China, we sent two of our people to the Chinese plant to work with them for a week; from the first batch, the product was in spec. including four weeks to evaluate suppliers, four weeks of tech transfer activities, and five-to-eight weeks for raw materials and lead times. the total time from project start to the first batch produced in China was about four months.

2

Product Y

This product was a recombinant-fusion protein entering Phase III clinical trials. This client had a partially-developed perfusion process and wanted production to commence simultaneously in Europe and Asia-Pacific. Their timeline was tight. We transferred the process from our client to our plant in Groningen, the Netherlands, and our plant in Brisbane, in Australia, scaling up production in both at the same time and writing half the batch records in each location. The total time from receiving the process information and ordering the raw materials to full production at both sites was four months—about 30-40% faster than the industry average.

3

Product Z

Product Z was a small molecule, lyophilized product. Our client wanted to transfer commercial production to our facility. Unfortunately, the technical data we received about the product and the lyophilization cycle (the freeze-drying process) was not sufficiently robust to guarantee a consistently high-quality product. In particular, we could see from the historical data that the lyophilizing cycle was not challenged at the edge of the critical process parameters (CCP), and there were several cake appearance issues even under optimum conditions. Instead of replicating the process as it was, we worked with the client to improve it, thereby getting the product right the first time, and improving both yield and quality over the prior process.

Why it works: A framework for successful tech transfers

Through the examples of products X, Y, and Z, we can see four important elements of our approach in operation.

1. Assessing risks and developing mitigation plans prior to transfer

To do that, we deploy a seven-step process we call the 7Ms. They are:

I. Machines, meaning their capacity, and the forecast analysis

II. Materials, taking into account such supply issues as lead time, availability, quality, and whatever supplier issues we foresee

III. Manpower, including staffing requirements as they are affected by demand fluctuations

IV. Manufacturability, which means looking at product issues and process robustness

V. Market, assessing the impact on volumes of competing products, as well as levels of market acceptance, among other factors

VI. Measurement, which models the boundary limits of the preceding five Ms

VII. Mitigation, in which we develop a thorough plan to manage the identified risks

A comprehensive risk assessment will yield a predictable set of activities on which a plan can be constructed. Such a plan allows all stakeholders to begin on the same page, ensuring the alignment of both the sending and receiving teams before the actual transfer. Furthermore, these steps generate thorough documentation of both process and product, making knowledge transfer easier and less vulnerable to informational gaps.

Once identified, those gaps can be filled, and steps that need to be improved can be identified—as was the case with Product Z's lyophilization cycle—and resolved before the transfer.

2. Fixing problems prior to transfer

As noted, our assessment of product Z revealed a weakness in the lyophilization (lyo) cycle, notably cake appearance issues. Accordingly, and together with the client, we performed a systematic characterization of the product and its formulation to understand better its behavior during lyophilization. We mimicked the lyo process in the lab, identifying the critical process parameters that were likely to vary in production, such as equipment performance, temperature, humidity, and time and velocity ranges. Then, in the lab, we measured the impact of those factors on yield, quality, cosmetic appearance, and varied them to see what changes produced the highest quality across all measures. In this way, we developed a more complete understanding of the factors that affected production and defined the envelope in which quality and yield would be optimal. During this process, we also were able to understand better the physical characteristics of the API, ensuring more reliable behavior in production, and limiting the impact of these variables on the drug product.

Fixing the lyo problem before the transfer enabled us to improve the process, strengthen the product's regulatory submission with the additional information we obtained, and created a strong relationship with our client that served us both well in this transfer and in subsequent ones.

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3. Standardizing processes and equipment

For the recombinant-fusion protein, Product Y, Thermo Fisher's facilities in Groningen and Brisbane essentially had the same upstream and downstream equipment—such as chromatography columns and skids—so we could be confident that what worked in one would work in the other. And not only was the equipment the same, but the two plants also have very similar operating procedures. For example, each plant operates the 500L perfusion bioreactor—a finicky process—in the same way and have almost identical standard operating procedures for common downstream processes. Consequently, batch records written for one plant could be transferred easily to the other.

We also made sure that the materials and supplies were already in both facilities' systems, so neither they nor their suppliers needed to be requalified, saving time and ensuring consistency and quality.

4. Paying as much attention to people as to process

Typically, the staff at the sending plant have expertise in a particular product and process. That, of course, should be captured in the documentation. However, even if it is, a specific answer to a problem may not be easy to find, and even with the best documentation, a nuance may go missing. The staff at the receiving plant may have deeper expertise in the type of product, or process, that can be applied to improve the existing process and streamline the transfer. However, sender and receiver can only help each other, and optimize the transfer, if their working relationship is close, collegial, and congenial. The single most important ingredient that makes that relationship work is trust. And trust emerges most reliably from successful collaboration.

For the Fc-fusion protein, Product Y, the teams at each of the two plants communicated in real time about progress, challenges, solutions, and so on. Joint project team meetings were held regularly, and communication between the plant managers was excellent. Given that all the communication was done remotely, it certainly helped that many of the people in the Groningen and Brisbane plants knew and had worked with each other previously.

If teams have not worked together before, partners need to take the time and trouble to allow trust to develop naturally through proximity. For example, for the API production step on Product X that we transferred to China, we assumed the not inconsiderable cost of sending knowledgeable people thousands of miles to the site. That was money well spent. It served to accelerate the knowledge transfer and when problems did surface—as they inevitably do—the receiving plant was not left to its own devices to try to solve or fix them without adequate support.

In the case of Product Z, we assembled a joint team with the client to work on improving the process, giving both parties time to get to know each other before the transfer. This paid off down the road as the team was able to work together productively throughout the lifetime of the product, supporting each other in matters concerning strategy, supply, distribution, and regulatory affairs.

"The single most important ingredient that makes that relationship work is trust. And trust emerges most reliably from successful collaboration."

Why companies are leery of technology transfers

As noted, technology transfers don't happen as often as they might, or as often as perhaps they should. Companies have legitimate concerns about supply interruptions and the costs they may incur as a result.

Then there is the expense. To plan a technology transfer thoroughly and execute it carefully requires a significant investment. To minimize the cost, companies are sometimes tempted to shortcut the planning and rely on what's worked before for similar products. This is a false economy. Looking at our history of transfers, we have found that the chance of getting them right by mimicking the transfer of a similar product are no better than 50%—a coin toss. Conversely, beginning fresh, with a blank sheet, and analyzing the process as if you have never done it before, the chance of right-the-first-time success is better than 90%.

Yes, technology transfers require investment. However, the cost is less than that of fixing one that went wrong.

In addition, a technology transfer provides the opportunity to make product and process improvements that might otherwise be missed. In practice, production processes often run for years without being improved meaningfully. Companies always have other priorities, including new projects, which steal attention from ongoing products. But in making a transfer, a company is forced to make changes; there will always be differences at the receiving site that need to be accommodated. Those changes—properly planned for and executed—can realize enduring strategic advantages by lowering production or distribution costs, or by improving a company's competitive position in a given market.

A challenge worth accepting

Transferring the production of sophisticated products from one site to another, or to several others, will always be challenging, and will always involve risk. But not only are there more opportunities today for companies to improve how they have their products made, there are also more options for securing supply, producing closer to critical markets, being more agile in responding to changes in demand, and securing sophisticated help with technically challenging production steps. Specialist expertise, solid processes, and standardized operating procedures and equipment all work together to minimize risk and costs.

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A consistent risk-based approach, continually updated with new data from quality by design and design of experiments initiatives, will improve the industry's ability to efficiently, effectively, and seamlessly transfer production going forward. The rewards can be substantial, and transferring technology should be an option every company places top of mind.

About us

Thermo Fisher Scientific provides industry-leading pharma services solutions for drug development, clinical trial logistics and commercial manufacturing to customers through our Patheon brand. With more than 55 locations around the world, we provide integrated, end-to-end capabilities across all phases of development, including API, biologics, viral vectors, cGMP plasmids, formulation, clinical trials solutions, logistics services and commercial manufacturing and packaging. We give pharma and biotech companies of all sizes instant access to a global network of facilities and technical experts across the Americas, Europe, Asia, and Australia. Our global leadership is built on a reputation for scientific and technical excellence. We offer integrated drug development and clinical services tailored to fit your drug development journey through our Quick to CareTM program. As a leading pharma services provider, we deliver unrivaled quality, reliability, and compliance. Together with our customers, we're rapidly turning pharmaceutical possibilities into realities.

Thomas Dax

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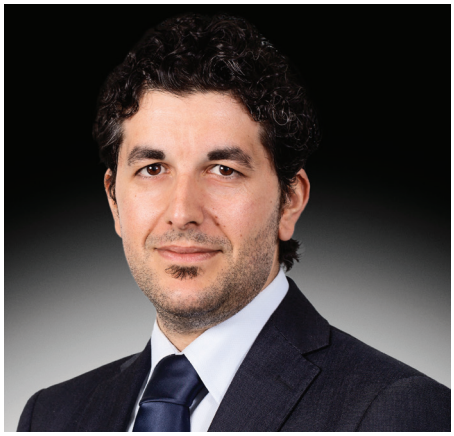
Thomas is leading Procurement Operations for Thermo Fisher Scientific's Austria site, including External Manufacturing & Outsourcing for Thermo Fisher's API manufacturing sites in Europe and North America. His professional experience is based on two decades history in the Pharma Chemical CDMO Industry. Thomas has held several leadership positions in Project Management, Process R&D and Procurement. He earned his Ph.D. in Organic Chemistry from Johannes Kepler University Linz.



Mirko Gabriele

Director, Technical Operations, Thermo Fisher Scientific

Mirko has held multiple leadership roles in technology transfer, business management and operations. Mirko started working as R&D scientist in API bulk manufacturing focusing on new drugs development and commercial process optimization, he expanded his experience and responsibility in the scale up of sterile products manufacturing from a site level and global level to land in operations such as production and maintenance. His experience includes Client relationship management, operations management, technology transfer, process development, process and equipment validation. Prior to joining Thermo Fisher, Mirko worked Chemi Spa. Mirko holds a M.D.in Pharmaceutical Chemistry from University of Rome, Italy and a Master in Business Administration in Pharma. He is QP certified and a PhD student in Biomolecular Science and Chemistry.

Paul Jorjorian

Vice President and General Manager, Biologics, Thermo Fisher Scientific

As the VP of Biologics Paul oversees a global Biologics Drug Substance manufacturing and development network for Thermo Fisher Scientific. Paul has held multiple leadership roles in process development, technology transfer and operations. In his career Paul has developed, transferred or manufactured over 75 biotherapeutic proteins at various clinical phases, including multiple commercial products. Experience includes business strategy development, operations management, technology transfer, process development, process characterization, and process validation. Prior to joining Thermo Fisher Paul worked for Bristol Myers Squibb and GE Plastics (now SABIC). Paul holds a B.S. in Chemical Engineering and Management from Purdue University, West Lafayette, IN and a Masters in Chemical Engineering from Cornell University, Ithaca, NY.

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