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# Using Technology Transfer to Maximize Business Efficiency

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**This article presents a technology transfer approach that can help prevent costly delays, leverage the ability to change, and speed time to market.**

## Introduction

In today's highly competitive marketplace, pharmaceutical companies must use their resources wisely. Often this means outsourcing production to other sites, both in the United States and abroad. As a result, successful technology transfer is more critical than ever.

Achieving success requires a paradigm shift. Traditionally, technology transfer teams were charged with moving a physical process from research and development into production. While that role remains critical, today's transfer team plays a larger part, helping the company attain its strategic goals throughout the product lifecycle. Systematically managing and sharing knowledge, prior to and during the technology transfer process, can help speed market entry. A scale-up operation is useless unless it can be leveraged in a business environment. From their vantage point near the end of development, as the product enters into commercialization, the transfer team is strategically positioned to capture information and provide feedback that can result in better market readiness - *Figure 1.* By sharing that information, the team can help the company begin the rise to peak sales. It is helpful to think of technology transfer as a knowledge transfer process – and to remember that it is not a stand-alone process, but a component in the drug development continuum.[22,26]

This article examines some of the elements – including development of a knowledge store and minimizing process complexity – that help elevate the technology transfer process to a strategic tool that can maximize business efficiency.

## The Importance of Shared Knowledge

"Continuous improvement" is not just a buzzword; it's a business practice. The more effectively knowledge is shared within an organization, the more efficiently the organization can operate. However, too often, information is gathered but not shared, and so it is limited in its usefulness.

Continuous improvement is possible through *incremental knowledge*. Incremental knowledge is gained through ongoing activities, and it grows with each transfer project. It can be as specific as the location of the new manufacturing facility or as broad as the idiosyncrasies of the production process. Incremental knowledge provides a basis for rethinking business processes as knowledge changes. Continually building on the existing body of information improves the quality of handbooks and Standard Operating Procedures (SOPs), reduces uncertainty, and moves the collective knowledge base forward.

As the body of incremental knowledge grows, the new information may then become *explicit knowledge* – that is, knowledge that can easily be set down in procedures, handbooks, or process maps. At the other extreme, *tacit knowledge* is not easy to codify or communicate. It is, simply put, "having a feel for the process." It may be, for example, an individual's knowledge that a process cannot run on certain days of the week due to manpower shortages. The goal is to build the store of explicit knowledge, because it is easily transferable. Such a "knowledge store" could include proven acceptable ranges for the production process as well as a manufacturing facility's specific capabilities – any information

that the company might need to access quickly at any point in the product lifecycle.

Explicit knowledge is not an exotic concept - it is the information that pharmaceutical development deals with every day: robust formulations, meaningful specifications, etc. Because it can save valuable time, explicit knowledge is cost effective. It results in a well-defined set of core technologies, speeds development and process introduction, and should serve as the basis of the team's work. The goal should always be to minimize tacit knowledge and enhance the explicit knowledge base, using incremental knowledge to continuously improve processes.

Knowledge transfer within a company can be called "organizational learning." Traditional means – such as handbooks, policies, SOPs, and even e-mail – can facilitate organizational learning, but additional means must be considered in order to share knowledge most effectively. Information technology tools such as groupware can facilitate knowledge transfer by combining, categorizing, and organizing information and making it available across teams.[1,2,3,4] To the degree possible, team members should meet face to face. Although this approach is not inexpensive, it may pay for itself in time savings, as potential issues surface readily and can be addressed promptly. For the same reason, consider assigning staff to the target transfer sites for process introduction.

The technology transfer team should represent all stakeholders, from development to engineering to production. Again, this is not a radical concept. Certain companies use cross-functional project teams or Chemistry, Manufacturing, and Controls (CMC) teams during the development process to bring all product knowledge, including clinical aspects, into one cohesive unit. The transfer team must take the same approach, as no one person knows everything necessary to prepare a product for market entry. The task is simply too complex. Although the clinical aspect may be out of scope here, the technology transfer team should include professionals representing supply chain management, packaging, and health and safety. In fact, consider consulting all disciplines that would ordinarily be needed to maintain a product on the market. However, the objective here is not to bring together a large, ineffectual team, but rather to form a focused group of point people who are supported by a well-chosen support network. Key members should represent tasks that are technically associated with the product. A secondary resource group can include those who play supportive roles during the product lifecycle and who can address most scenarios that the core transfer team is likely to encounter. Identifying these resources at the outset gives the transfer leader the ability to quickly address any hurdles that arise along the road to market entry. For example, some companies have selected market packages that were not known to all stakeholders in the supply chain, placing the outcome of the transfer at risk and missing tight timelines. A multidisciplinary team that systematically shares knowledge can help prevent such potential obstacles. The team creates the knowledge store – a resource to which all may turn for direction.

Remember that learning occurs not only within teams and across teams, but from the market. The importance of market learning – gained by monitoring competitors via industry news and regulatory citations – should not be overlooked. For example, take the company working on a bilayer tablet formulation. The knowledge that a competitor faces regulatory action due to delamination on a similar formulation is a critical piece of business intelligence. The information should drive the company to modify its approach to the outlining of the product's quality attributes. Critical analysis of the information might even direct the company to adopt unique in-process controls.[11,17, 21]

## Start Early to Build a Robust Knowledge Store

Ultimately, the knowledge store – explicit, optimized knowledge of the product and processes – drives successful technology transfer by reducing uncertainty and accelerating the transfer process. What elements should the knowledge store include? How should it be developed?

Compile data as early as possible in the development cycle and use it to establish a technology strategy that will qualify change in the context of scale-up or site transfer, as well as possible post-approval changes. This approach can speed both product development and product approval. Be sure to focus on data that protects the patient, i.e., critical quality attributes, and assures that the process is under control, bearing in mind that the two are not necessarily related. For example, with a high-dose tablet, nine times out of ten, the assay is not as important as the weight. Depending on the dosage form, the drug substance and its Biopharmaceutical Classification System (BCS) classification, creating an *In Vitro*/*In Vivo* Correlation (IVIVC) may benefit formulation and process optimization and the creation of meaningful specifications. Investing time and money to establish IVIVC will allow the company to move quickly without having to conduct subsequent human kinetic studies prior to technology or site transfer, ultimately shortening time to market.[6,10] Of course, the IVIVC will be specific to the formulation, and thought must be given to where in the development cycle IVIVC will be established.

To establish the IVIVC early in the process, use blood profile data from "discovery phase" studies as a starting point for dissolution work. Even if it is from animal studies, it provides a direction. As the formulation is optimized, continually refine and validate the data and add it to the knowledge store. During scale-up, the dissolution data can be used to judge the impact of process changes as well as to establish final specifications for dissolution. Anchoring specifications to human kinetic data provides reliability and a guidepost to make defendable changes regarding the site or the process.

However, be aware that the use of a sound pharmacokinetic basis for setting specifications and establishing a reproducible process alone is no guarantee of success. For example, one company was producing a modified release product. The product passed an US FDA Pre-Approval Inspection (PAI) with no issues, only to have a commercial manufacturing

failure rate of 10% at maximum output. Three batches were produced for the PAI with no problems, but at high output, the process disrupted the product's polymeric coating, and the product failed to meet critical quality attributes. Availability of explicit knowledge concerning the method of handling the bulk product would have prevented this problem. In this case, a champion from the launch site at an early stage to help other team members understand the commercial implications would have been the best way to grow the knowledge store.

To continue building the knowledge store, use process development as a platform to establish proven acceptable ranges. Doing this provides a historical database for the product and a basis for statistical process control. Companies that fail to develop and systematically catalog proven acceptable ranges often stall in a pre-approval inspection, because they cannot readily access the information necessary to answer the FDA's questions – even if the information exists.

Start with broad ranges during early development and revise and refine them through Phase I and clinical trials. Use a systematic reporting method and reference it with every change from pilot scale, through scale-up and validation. Simple tabulations at the beginning of process development will prevent huge problems later.[23]

To establish proven acceptable ranges, create a chart for all process steps and controllable parameters, along with a brief description of each. Record the engineering units, and document the anticipated result of exceeding the proven acceptable range. Evaluate whether the risk of exceeding the range is major or minor. It is minor if it represents no risk to the patient. Documenting this risk assessment serves as a "bulletproof vest" by backing up the information in the primary documents, such as product development reports, justification of specifications, and validation reports. For each parameter, establish the operating range to be used in the plant for process control. Acceptable ranges that depend on scale changes, such as the number of spray guns or fluid bed dryer air volumes, can be listed as "to be determined."

As a final step in building the knowledge store, completing technology transfer through validation may be an expedient way to assure rapid market entry. Just to be clear, all facilities, equipment, and critical systems must be fully qualified before executing any product validation. Validation demonstrates control over the process and finished product, ensures compliance with internal and external requirements, and adds to the knowledge store. Bearing in mind the Quality by Design initiatives and the guidance of ICH Q8 and Q9, the manner in which the company is going to file will determine the nature of the validation. However, for the foreseeable future, the majority of filings are likely to follow the three-batch validation paradigm. Regardless of whether the company files a currently accepted submission or opts to adopt Quality by Design, creation of a solid knowledge store is imperative – and grounded in current industry practices. Ultimately, the forward-looking approach necessary to build a knowledge store will support a company's adoption of Quality by Design, which is firmly rooted in knowledge management.

Although not required, completing validation prior to a submission may expedite market launch. While this view may not be acceptable to generics companies, small companies with limited drug substance supplies, and others who do not include validation in their business plans, validation is one step in the journey to 100% business efficiency and peak sales.[9,21] If a process and product are already validated, production can launch within two days of registration approval; otherwise it might take six to nine months to ramp up production. In that time, the competition might already have gained a large share of the market. To assure a rapid path to validation, use a risk-based approach that balances good science and common sense. Rate each process step as having a high, low, or no impact on product quality.[7] For clarity, use Scale-Up and Post-Approval Changes (SUPAC) equipment terms. For example, the critical area checklist for a film-coated tablet may include:

- Weighing/addition of raw materials
- Pre-blending of materials
- Granulation (speed, rate of addition, time)
- Drying (temperature, time)
- Particle size reduction
- Blending/lubrication
- Compression
- Coating

Record data related to the items on the critical area checklist and review them for traits and atypical behavior. Showing the data graphically makes it easier to identify process variability within established specifications, in other words to compare processes.[5,8] Defining these critical areas, their endpoints, and their impact saves time and effort when designing the validation strategy and the process parameters going forward. Once the information is compiled, it is possible to look at expected parameters and atypical behavior, and then identify realistic ranges for statistical process control during the product lifecycle.

As the new drug development clock ticks, the Pre-Approval Inspection (PAI) is clearly a key milestone - but it does not stand alone. The largest strategic mistake a company can make is to think of development, regulatory submission, transfer, and PAI as separate and unrelated events. A good transfer team ensures that all these aspects are addressed clearly and logically in a deliverable that is consistent with the regulatory submission. If the team has followed the approach outlined here, capturing and sharing explicit knowledge from the early stages of product development, then the team will be prepared, and the transfer and subsequent PAI become steps in a seamless continuum that lead toward market dominance.

During the PAI, the FDA investigators look at drug substance characterization, process procedures, in-process tests, finished product specifications, dissolution profiles, and stability.[12] If the launch site is detached from the development site, the investigators may audit both. If the knowledge store has been well defined, the information that the investigators

need is readily available. Any issues that arise can be addressed quickly. Having the product information recorded and available during PAIs will prevent delays and expedite product launch. The other key advantage of a well-developed, well-utilized knowledge store is that it can facilitate communication between the transfer and the CMC teams. This helps ensure that the inspection is seamlessly aligned with the regulatory submission – so the reviewing chemist sees the same information as the field inspector does.

## How to Share the Knowledge Successfully

Building a knowledge store can provide significant benefits throughout the technology transfer process and beyond – but only if the knowledge is shared and utilized. Whether the product is being transferred to an existing group company, a contractor for custom manufacturing, an established company through collaboration, or to an expansion facility, two things are vital: good communication and a streamlined technology transfer process.[20,24]

The technology transfer team is charged with getting from A to B in the shortest time possible so this is no time for complicated studies. To minimize process complexity, establish the *same process technology* at all manufacturing sites. For example, it would not be advisable to attempt to go from high-shear in a bottom-driven machine to high-shear in a top-driven machine without considering the full impact and possible downside. In those considerations, team members must look beyond their specific activities. Establish a common technology agreement between the launch or production site and the development area and integrate the agreement into the transfer strategy. This will accelerate process introduction and enhance core capabilities. It also makes it possible to source Phase III supplies.

Wherever possible, combine efforts such as site qualification and operational qualifications data for the process; use the final market image. As noted above, avoid radical process changes, and use the SUPAC equipment guide to establish sameness of equipment and process. Develop processes using a sub-batch concept. For solid dosage forms, this reduces validation and supplies a defendable basis for change in scale. For example, in a wet granulation process, granulate in two sub-batches and then blend out in one. For scale up, change the size of the blender with a commensurate change in the number of sub-batches.[15,16]

Remember that technology transfer is an "away" game that is likely to be played out in an environment with different rules. It is important to know the culture of the transfer site. Each organization, and each site, has an integral pattern of behavior and thinking, a way of doing things that makes perfect sense to that particular group. An aberration – such as a speck in the color – that one culture, e.g., the sponsor, might consider a minor variation, might be viewed

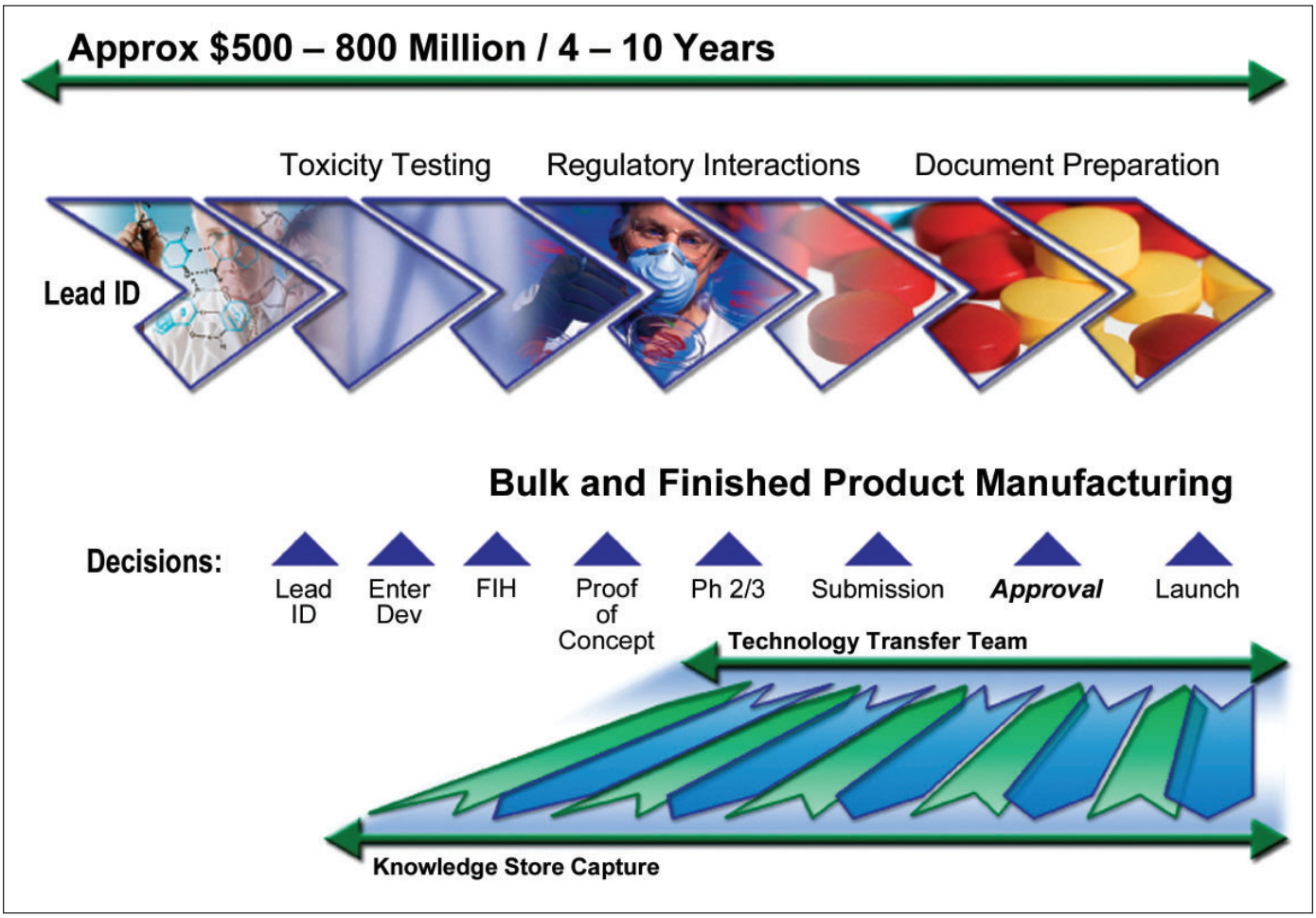


Figure 1. Drug development and technology transfer.

by the other (e.g., the contract manufacturer) as a reason to stop the batch. It is important to establish upfront whose philosophy will dictate the manner in which the batch will be processed. These cultural discussions should not be adversarial, but they should be held early. There should be a two-tiered approach – one is the contractual agreement and the other is the daily working agreement. Agreements must be shared with all transfer team members.[13,14,18,19, 25]

Prior knowledge of the infrastructure also is important, especially if production is transferred to another country. Ensure that the supportive infrastructure extends beyond Quality Control (QC) and Good Manufacturing Practices (GMP) to include a range of other crucial factors that cannot be taken for granted. Otherwise, the project may be headed down a path to disaster, regardless of whether the product is a tablet or a semi-solid. For example, does the site have potable and purified water? Most pharmaceutical engineers have encountered facilities that shut down during certain times of day because there is no water. Does the site have adequate steam pressure and capacity? Does the dryer work within our desired range? Can two dryers run simultaneously? What about Heating, Ventilation, and Air Conditioning (HVAC)? Don't assume that the availability of air conditioning means that the facility is cooled 24/7. A building that is only air conditioned Monday through Friday is not a good choice for production of a product that is affected by heat. Is the waste management infrastructure adequate for the manufacturing capacity? In one recent scenario, the transfer team inspected the transfer site, observed floor drains and assumed that waste would be adequately handled. After introducing the product, the transfer team returned to the site and observed that wastewater was being drummed. They found that the effluent amounts exceeded the treatment plant's capacity. The company was now financially obligated for a $15 million waste treatment facility upgrade, a cost that was certainly not part of the initial plan. The transfer team was at fault, as no one had asked the key questions during the initial site visit. Clearly, lack of knowledge can lead to disastrous consequences.

Other factors that may hamper successful transfer of product include insufficient labor pool, inaccessibility of the plant, registration with local agencies, and communication and language barriers. In a validated environment, a smile and a nod are simply not adequate communication. It also is critical to establish what would happen in the case of a business interruption due to a facility disaster such as fire or explosion. Is the facility covered for these scenarios and who is liable?

Finally, while it is not always feasible to assign a team member to the transfer site, do it whenever possible. As noted above, nothing is more important in a successful technology transfer than on-site inspection of the facility and face-to-face communication with the team.

## Conclusion

The essence of technology transfer is transferring the knowledge and understanding of the process from one site to another. It is not an end in itself, but part of a larger process that begins with product development, assures business efficiency and peak sales, and follows the product throughout its lifecycle. Along the way, building a knowledge store that can be refined and shared allows for continual improvements and facilitates technology transfer. To develop this knowledge store, it is necessary to minimize tacit knowledge and maximize codifiable explicit knowledge. Begin to build the knowledge store during early development, and refine it with lessons learned from internal processes as well as competitor and market information.

In addition to gathering data and documenting the product and process, it is important to know a great deal about the transfer site. Discuss each site's culture and agree as to which will be the driver, and wherever possible, plan for site visits and face-to-face meetings.

The additional time and effort involved in the approach described here can not only facilitate technology transfer, but can help prevent costly delays, leverage the ability to change, and speed time to market.

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