

# Pharmaceutical MANUFACTURING

## *Don't Fumble the Tech Hand Off*

**E**very pharmaceutical process experiences one or more technology transfers during its lifetime. Each time, critical process knowledge moves from one group or organization to another.

Whether a transfer occurs according to the most exquisitely planned protocols or through the sledgehammer approach, it will, in the end, get done. Technology transfer is more of an indicator of overall manufacturing excellence than it is a predictor of anything larger.

But today, technology transfer's significance is magnified as more products, particularly biologics, are outsourced through alliances and manufacturing-only relationships. "Increasingly, tech transfer is becoming a core competency for companies developing novel therapeutics," says Matthew Hudes, a managing principal with Deloitte (San Francisco, Calif.). "In the past, not that many companies recognized that."

Even the most successful companies wrestle with these problems. Genentech is one firm that Hudes believes has mastered scaleup and tech transfer, both internally and with its partners and contractors.

Although the functional aspects of tech transfer may be similar in customer-vendor arrangements, between partners, and within an organization, the incentives are aligned differently. Processes

**Technology transfer was once taken for granted as something that would "get done anyway."**

**Now it's an indicator of manufacturing excellence and a core competency for drug innovators**

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are likely developed by innovators and handed off to CMOs who are tending to other business. With more "skin" in the game, partners tend to become more involved in process development.

An incomplete or incoherent commercialization path, and lack of predefined success criteria can strain relationships between tech transfer partners. For example, a "great" chemical process can be a non-starter when ramped up to a larger scale. Something as simple as an excipient's not being commercially available can ruin the transfer. More likely, performance metrics, particularly in-process analytical tools, lack the appropriate resolution and discrimination at larger scale. Poor manufacturability has sent more than one CMC filing back to the drawing board.

When it comes to transferring a product or process, the originating group or company must consider every material and activity. Even such basic components as the material used to manufacture a delivery device can throw roadblocks into the scaleup and tech transfer pathway. According to Bikash Chatterjee, president of PharmaTech Associates (Foster City, Calif.), a consultancy for regulated life sciences, drug delivery systems are a common source of trouble. Increasingly, sterile injectible drugs use novel delivery systems whose materials of manufacture lack adequate regulatory documentation as to compatibility and chemical stability. "If the manufacturer of the polymer used to make the container won't divulge how the material was manufactured, you can't file the product." An even worse scenario occurs when an entire development program is based on that particular delivery vehicle.

Companies successful at tech transfer practice extensive upstream characterization of their molecules. In biotech, this means heavy reliance on design of experiment exercises to model large fermentations. The industry has invested in technology for producing robust, qualified, validated models at the 10-100 L scale that precisely mimic much costlier 10,000 L cell cultures to convince the FDA. "Without data," says Chatterjee, "it's very difficult to tell your story."

Developing such models requires top-level science and documentation, which, not coincidentally, supports biopharm's growing reliance on tech transfer to contract manufacturers. According to Chatterjee, that is a good practice. However, as CMOs get busier, relying on them to do development work will become a less attractive proposition.

## **PLATFORM APPROACHES SMOOTH THE TRANSITION**

Pharmaceutical and biotech manufacturers have long appreciated the value of adopting platform technologies whenever feasible. Advantages include greater familiarity with unit operations, heightened confidence in the ability to deliver quality product and better deals from vendors for equipment and disposables.

Platform technologies and processes also facilitate technology transfer. The biopharm CMO Avid Bioservices (Tustin, Calif.), a subsidiary of Peregrine Pharmaceuticals, specializes in stirred tank cell culture for monoclonal antibodies. Avid uses CHO cell fermentation, Lonza's Glutamine Synthetase expression system, CD-CHO cell culture media from Gibco, disposable harvest systems from Millipore and, whenever possible, the same harvest, capture and purification steps for most of its approximately ten ongoing projects. The company uses batch fermentations, but is investigating perfusion reactors to improve volumetric throughput. Provided they do not insist on a home-brewed process, customers know what they are getting every time. The unit's operations are plug and play, so even when customers insist on bringing in home-brewed technology for some steps, platform operations can be woven in.

The platform approach works with scaleup and transfer of process analytical technologies (PAT) as well. Earlier this year, John Grosso, Ph.D., an executive director for Bristol-Myers Squibb's (BMS) analytical R&D department (New Brunswick, N.J.), presented a talk at the IQPC Forum on technology transfer and PAT. BMS considers PAT not only an agent for tech transfer – Grosso

placed it at the "interface" of this process – but tech-transferable in its own right. "Migrating PAT is the focus," he says.

The "scalability" of PAT becomes an issue during tech transfer. While offline or at-line analytics such as liquid chromatography are usually scalable (for example, it makes no difference to the chromatograph whether one is sampling a 5 mL round bottom flask or a 1000-L reactor), the same is not true for embedded analytical probes. Batch homogeneity, sensor placement and off-target variables like temperature and pressure can affect measurements.

BMS evaluates each product and process individually, weighing the benefits against the investment in PAT infrastructure, training and implementation. Safety is a major benefit. "If a PAT sensor reduces exposure to a toxic or potent API to zero, it's easy to build a business case around its implementation," Grosso says. PAT also makes sense when measurements critical for process understanding are inaccessible through conventional measurement techniques.

BMS recently deployed PAT, using Raman spectroscopy as the analytical method, within the process for manufacturing Sprycel, a tyrosine kinase inhibitor for treating chronic myeloid leukemia that was approved in June, 2006. Factors in the PAT tech transfer included the reliability of data between different instruments in moving from development to manufacturing, and the positioning of sensors in the reactor train. "As you gain more experience with PAT, you recognize these as standard issues," says Grosso.

## **SIMPLE OPERATIONS, COMPLEX ISSUES**

Baxter BioPharma Solutions (Round Lake, Ill.), which contract-manufactures premixed parenteral drugs in flexible plastic containers, has become a specialist in frozen premixed drug products. Based on the drug's stability, the premixed products are either aseptically processed or terminally sterilized. Some products are frozen to enhance stability

during shelf life. Products include penicillins, quinolones, cephalosporins and other sensitive molecules.

Development, scale-up and transfer of frozen-premixed processes entails sophisticated process controls for temperature, processing times, component addition sequence and rate of addition. For these products, critical operations include mixing, filtration, filling and sterilization.

Even seemingly uncomplicated chemical transformations involve tech transfer issues. Neutralization is straightforward enough at laboratory scale, observes Rao Chilamkurti, Ph.D., who heads Baxter's Pharmaceutical Technology group. "But when we scale up to batches ranging from a few hundred to 20,000 L, we begin to see solubility and stability problems that may result in unacceptable levels of impurities and byproducts."

Neutralizing an acid form of an active pharmaceutical ingredient (API) with sodium hydroxide works, but this strong base can react with the drug when it is added too rapidly. A milder base, sodium bicarbonate, generates carbon dioxide that must be removed from the final formulation.

API particle size is usually not a consideration with drugs going into solution, but if the drug is not very soluble, larger particles take substantially longer to dissolve than smaller ones. "These issues are quite difficult to pick out at lab scale, but at 1,000 L they can be critical," says Chilamkurti.

Not every tech transfer operation is fraught with peril. According to Chilamkurti, filling, filtration and sterilization may be considered "platform processes" that transfer readily, with minor modification, between products and scales. Another relatively easy transfer involves changes of formulation pH to confer stability or solubility. "This can be done at lab level and reliably ported to manufacturing."

Baxter's scale-up and tech transfer process begins with the identification of "formulation activities" at the lab level. This provides a basic understanding of

## **BEST PRACTICES IN TECH TRANSFER: SUCCESS HINGES ON MULTIFUNCTIONAL TEAM EFFORTS**

Successful technology transfer originates from a dedicated, multidisciplinary tech transfer team assembled as soon as the product enters development. This group, consisting of quality, engineering, supply chain, development, QA, QC, regulatory and operations personnel, is actually easier to put together at a small pharm/biotech company where professionals wear several hats. "Larger firms tend to have a lot of specialty silos," says Chatterjee of Pharma Tech. For the duration of the project, team members report to the project leader rather than to their functional managers on tech transfer matters.

Chatterjee also warns about expectations gone awry during tech transfer. Unless they have manufactured the product themselves at full scale, even top companies may have difficulty understanding cost escalations as batch sizes increase. This disconnect with reality most likely will occur when transferring a process to a CMO. "The manufacturing line may not be the same for commercialization as for Phase III," he says.

According to VaxGen's James Panek, a successful tech transfer project demands that scientific and technical personnel from the originator company be present at the technology transfer site, especially in the early stages and during initial full-scale runs. "Those are the people you need to talk to when something goes wrong, or if there is a question about how to carry out an operation. It's very difficult to get those answers from QA/QC or project management." He describes projects where process questions are answered by an intermediary as like a game of telephone. "You may not get the answer to the question you're asking, and even if you do, it is not in real time."

Panek also suggests maintaining an updated project plan, so all the principals know exactly where the project stands within the timelines and whether milestones such as fill date, regulatory filing or clinical trial start will occur on time. A technology transfer project plan consists of a detailed list of operations broken down by task. "When things happen, you check them off and everyone is assured the timelines are met." The plan may be annotated or supplemented with appropriate documents (e.g., a drug development or substance characterization report). Each component should include metrics for assessing progress, quality, completeness and completion. When communicating the plan to a client, a CMO should construct a timeline that is as detailed as possible, listing every item and its expected duration.

"Communication" has become cliché in discussions of pharma collaborations, but it cannot be overstressed when transferring technology to overseas manufacturers. "Tech transfer issues are multiplied as you enter the global CMO sphere," says Matthew Hudes of Deloitte. BMS's Korean venture is perhaps an extreme example, but cultural and other issues arise as a function of geographic distance. Companies with the resources can overcome these issues by forming global technology transfer centers of excellence, where scientists and engineers can exchange process knowledge.

A common mistake during scale-up and technology transfer is an under-appreciation for the impact of batch volumes on mixing, and ultimately product quality, for sterile, pre-mixed drug products. Temperature, mixing time and the sequence and rate of addition can greatly affect degradant formation, as Baxter's Chilamkurti points out. On the other hand, compared with solids, solutions have more predictable physicochemical properties. Dissolved drug formulation processes are therefore easier to transfer from R&D to manufacturing or to a contract manufacturer, and simpler to scale.

Another impediment to smooth tech transfer is the reluctance on the part of innovators to provide full details on the drug, its physical properties, formulation, analytic information and manufacturing details. Many companies adhere to a "need to know" policy with respect to contract manufacturers. However, what the manufacturer needs to know is not always obvious.

Processes and unit operations benefit from easily-transferred "platform" deployments of process analytical technologies (PAT). For PAT to be effective, engineers must test the systems with many process variables to be sure it will behave during normal operation. It may not be possible to predict these variations during PAT tech transfer, due to slightly different reactor configurations, agitation, heat transfer and other variables. "This is not plug and play," says BMS's Grosso, who estimates that only 50-75% of the knowledge gained from one Raman PAT deployment is directly transferable to a second process.

materials and equipment. During this evaluation stage, the Baxter tech transfer team interacts with the innovator company, engaging in as much scientist-to-scientist or engineer-to-engineer interaction as possible. Tech transfer begins at the manufacturing plant through the manufacture of a series of test batches. Baxter first produces an evaluation batch in commercial equipment to learn as much as possible about process parameters. Next, additional batches are produced for stability evaluation and process validation. During this time, applicable formulation and analytical technology is transferred from Baxter R&D to its manufacturing plants.

### **NOTHING BEATS FACE-TO-FACE COMMUNICATION**

The entire process is facilitated by interaction between Baxter personnel and scientists and engineers at the innovator company, who typically travel to Baxter

plants along with their own tech transfer team to facilitate these steps. As Avid's Richard Richieri puts it, "You can write as many reports as you like, but nothing beats a face-to-face meeting."

Sometimes the personal approach is not enough, such as when transferring a process to an untried manufacturing partner. James Panek, Executive Vice President of VaxGen (Brisbane, Calif.), who is responsible for the company's manufacturing operations, recalls one challenging case, involving the transfer of cell-culture technology for a blockbuster rheumatoid arthritis biological product from a major U.S. pharma to contract manufacturer Celltrion (Inchon, South Korea). Celltrion runs the process in four 12,500-liter bioreactors and is planning a significant capacity expansion for this and other products.

In the transfer of general cell-culture technology, VaxGen participated with Celltrion in designing the fermenta-

tion facility, providing expertise on specific processes and in-house training, including visits from Celltrion scientists to VaxGen's manufacturing facility in Northern California. Later, VaxGen facilitated the technology transfer of the rheumatoid arthritis drug. The process for the drug is "extremely robust," Panek says, using standard Chinese hamster ovary (CHO) cell lines. Purification also is standard, relying on a capture step, flow-through chromatography, tangential flow filtration and a polishing filtration step.

Founded in 2002, Celltrion was in full operation and secured its first major customer in just three years. The company's success relies in part on its accurate prediction of a worldwide shortage of cell-culture manufacturing capacity. "Celltrion has become a model for what can be achieved in technology transfer and large-scale biopharmaceutical manufacturing," says Panek.

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