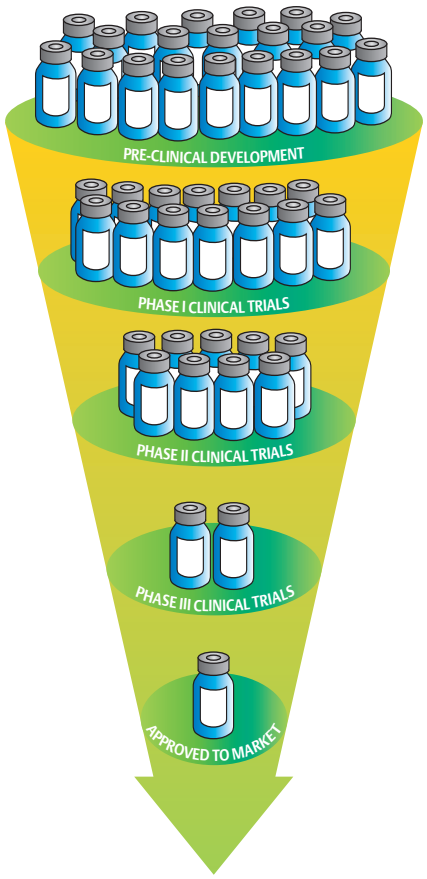
Making Technology Transfer Painless

Taking a potential molecular or biological entity from research and development to market can be challenging for even the most experienced life sciences companies. In addition to the product development work, it requires collecting, organizing, and transferring the masses of information required to define a product, produce sufficient quantities of a candidate, satisfy regulatory agencies, and obtain the necessary licenses. Simply satisfying the basic requirements is very costly and time consuming.

The sheer volume of information can be daunting. Moving an ever increasing amount of data from R&D through the various stages of testing, licensing, and commercialization is a huge responsibility where problems can derail even the most promising products. Frequently, the transfer of technology is accomplished by means of written protocols, aggregated data, and reports that leave room for misinterpretation. However, by employing high-level knowledge management techniques and a common set of communication tools, transfers of technology can be accurate, effective, and efficient, thus reducing product development costs and shortening the time-to-market.

Tufts University Center for the Study of Drug Development conducted a study that is summarized in the Standard and Poor's Industry Surveys Biotechnology, August 13, 2009. According to this study, it can take as long as 15 years and as much as $1.2 billion to move a drug from pre-clinical development to bio-



Business process efficiencies are needed to reduce overall drug development costs.

pharmaceutical product market launch. Even excluding the financial drain of drug development failures and associated time expended, the cost remains at $559 million per biologic.

Obviously, any viable method of efficiently pushing potential products through the maze of requirements, hastening the elimination of unacceptable candidates, and shortening elapsed time before a product is commercialized will have a dramatic impact on a company's R&D costs and bottom-line profitability.

R&D to Clinical

Product innovation is difficult in any industry; however, life sciences companies face special challenges inherent with the complex sciences that are the bed rock of the pharmaceutical industry.

Research begins with hypotheses on how certain candidate entities should react in the body. The candidates that show promise against a particular disease are produced for pre-clinical test tube and animal-based experiments. Promising candidates are submitted to the appropriate regulatory agency for recognition as an investigational new drug (IND). Upon acceptance, sufficient quantities of the candidate material must be manufactured to support three phases of clinical trials from which affirmative data must emerge to qualify for licensing.

Phase I consists of safety dosage testing of healthy humans; Phase II includes placebo-controlled efficacy tests of persons with the condition; testing for license submission concludes with Phase III studies with placebo control of persons with the condition; and many molecules run into Phase IV to track safety or extend the indications for the molecule.

Several additional complexities straddle the pre-clinical and clinical phases of drug development including toxicity and pharmacokinetics. Models for determining dosage, buffers, and coatings are key outputs of these

complex sciences. Associated documentation can be voluminous.

In pre-clinical manufacturing, additional experiments lead to identification of significant process parameters, set points, and control variables. During this stage, data from successful product runs are analyzed in order to define operating ranges for critical process parameters. This information is often manually reviewed, summarized, and transferred at each step along the path to commercialization. Such manual systems do not easily accommodate the safe and effective transfer of information.

After all this hard work is completed an abundance of supporting data is submitted for approval. For chemical-based and therapeutic biological products an NDA (new drug application) is submitted to CDER (Center for Drug Evaluation and Research). Vaccines, blood, and tissue-based products must have a BLA (biologics license application) filed with the CBER (Center for Biologics Evaluation and Research) for approval to produce and market.

A growing and highly complex package of information must be managed throughout the entire new product evolution. Typically, a program manager shepherds the project including information transfers from research through production, working with all of the subgroups (R&D, clinical, pharmacokinetics, toxicology, etc.) involved in creating a new product.

Clinical to Commercial
Following initial regulatory approval, the actual production process is often scaled-up from pre-clinical manufacturing to a larger, more GMP-compliant clinical manufacturing area.

Technology transfer challenges to be overcome:

- Collecting and analyzing data
- Copying and pasting or taping important info (chromatograms, for example)
- Summarizing and understanding process changes and batch records throughout development
- Summarizing data to support transfer protocols, reports, and regulatory filings
- Defining critical parameters, operating ranges, set points, and control strategies
- Communicating general warnings and known issues about the process
- Optimizing yield and meeting quality standards by minimizing variability

As the process to manufacture a particular product is developed, data are accumulated using laboratory notebooks and automated or non-automated data collection systems. Experiments are defined and executed while in-process data and samples are also collected. Sample results are recorded after relevant tests have been completed. For some assays, test methods must be developed before the sample can even be evaluated. So, the scientists and engineers are working to define experiments to be conducted, collect and correlate data, assure batch context of data, define the process, and optimize process parameters. Alterations made during process runs must also be documented, understood, and managed as part of the total process history.

A clinical trial protocol must be submitted to the regulatory agency (or agencies) prior to commencement of any human trials. After a campaign is completed to support the clinical phase, the manufacturing data including processing parameters, in-process and release testing results, recipe or batch record information, and materials information are summarized in a report. This along with the actual clinical trial data is used for product licensing applications.

Then, the transfer to commercial manufacturing can begin. Testing ranges and results from the experimental runs and clinical trial runs, batch record summary information, potential process descriptions and parameter ranges, and all supporting manufacturing data are compiled and used to form the protocol for commercial manufacturing. After Operations successfully completes the number of lots required in the protocol, unit operations, set-points, critical process parameters, operating ranges, experimental ranges, and batch instructions are refined. The processing data, materials information, and validated test results are summarized in yet another report. All of the information must be available to support pre-approval inspections (PAI) and licensing for the facility.

Challenges of Technology Transfer
Technology transfer is an iterative process of moving information from development to manufacturing. This involves disseminating known information about the product and anticipated process, collecting and analyzing test results, defining and executing experimental batches and campaigns, gathering process data, and providing summaries. Inputs consist of what is known about the product and the process

at the time – data from prior similar products, research data from lab notebooks, characterization studies, batch instructions, set points, experimental data, and a campaign plan. Outputs consist of executed batch records, processing data, and test results, generally in the form of written reports – often hundreds of pages long. These huge, often repetitive documents must be reviewed and understood in total.

Without a common vocabulary and a shared set of tools, technology transfer can be particularly frustrating. Extra effort is required to deal with variations across the network sites, inconsistent terminology between groups, and disconnected sets of information needed to support licensing a marketable product. This can create costly delays due to inconsistencies, errors, and poor translation of data introduced by each successive group.

Each site often has unique methods for managing similar business and production processes, even for the same product manufactured at two commercial sites within the same company. Additionally there are differences between equipment at the sites supporting technology transfer through the development lifecycle. This can be particularly trying when equipment characteristics, piping, valves, instrumentation, and automation algorithms differ at each step along the way.

Equipment differences may be overcome with appropriate engineering and scale-up techniques. Piping, valves, and instrumentation differences as well as business process differences are handled with batch records and standard operating procedures specific to a site. Automation is generally developed for a specific site, sometimes starting with a library of objects. So, differences from site to site may eventually be overcome with a lot of hard work by the project, quality, technology, engineering, and automation teams. Of course, this contributes to the ever-growing volume of information moving along the path from development to commercialization.

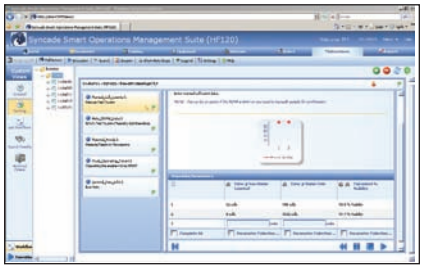
Whether technology transfer efforts are managed within a site or between sites, these efforts between groups share neither a common language nor a common set of tools. The need to translate the language and associated knowledge between groups creates an inefficient process that inherently introduces the opportunity for error. Since each group is working in a somewhat isolated domain with its own processes, the knowledge is situated in that domain rather than in a common expression. The lack of shared tools only reinforces that sharp line between groups, and emphasizes the need for data migration and developing automated structures from scratch. In addition, due to these differences, a non-value added review loop is required for the experts on each side to verify the accuracy of the knowledge transfer.

Solutions

According to an economic study sponsored by the National Institute of Standards and Technology and reported in Standard and Poor's Industry Surveys Biotechnology, August 13, 2009, between 25 and 48 percent of R&D expenses can be saved through improvements in technology infrastructure, standardization of data collection, and quality control for post-market surveillance. A significant reduction in development and approval time of biopharmaceuticals is also possible.

A shared set of tools can help break down those barriers by allowing the various groups to exist in a common authoring environment, and, more importantly, provides the means to hand off knowledge, data, and design without the need to translate or transcribe.

Reusability is an inherent feature in Emerson's Syncade™ Smart Operation Management Suite and DeltaV™ digital automation system. The Syncade software suite provides flexible, integrated solutions for resource management, operations optimization, and integrated information, while meeting quality and compliance requirements and improving operations performance. By using the latest technology and adhering to accepted best practices, this solution reduces engineering, testing, and maintenance costs. Syncade Suite supports sustainable manufacturing practices by reducing waste, conserving paper, and eliminating errors.



Syncade: Operations management visualization to streamline technology transfer processes.

Reuse of work instructions, phases, operations, unit procedures, and equipment modules/classes are key capabilities of both Syncade and DeltaV. By utilizing these solutions, biopharmaceutical companies can aggregate large amounts of data electronically for reporting, justifying, and licensing requirements. These shared tools reduce the language translation problems and help to mitigate the design hand-off issues.

In addition, shared tools enable an organization to focus on the five or six things that are really important

to a particular process. The end product can be measured against truly critical process parameters. This focus on critical parameters is fundamental to PAT (process analytical technology) of which Emerson is a leading proponent.

Emerson is now partnering with Optimal Industrial Automation to use SynTQ – a product that can interface with many analyzers and high-powered data analysis tools as well as control systems. Syncade extends the capability to track data, recipes, changes, and vital information back into the design space. Since Syncade has the ability to communicate with other systems in an established protocol known as B2MML, interfacing with electronic lab notebooks, for example, can become reality, reducing errors of transfer and creating greater traceability of knowledge.

When a production process is under development, the scientists and engineers may not know exactly how they want a particular process to run (down to all the parameters) until they are actually underway. Yet, they need the flexibility to make changes through start up and rapidly modify production records with a documented, understandable rationale supporting the licensing application.

The generic recipes, audit trail of configurations, and process analysis tools found in Syncade Suite are helpful in successfully managing many challenges.

For example, recipe authoring tools enable scientists to build an outline of the process and then add layers of parameters to create a general recipe where a development recipe morphs into the master recipe over time (without transcribing). Some of this is currently possible with parameterized recipes in Syncade and work is underway to carry the technology to the next level.

The use of technology to aid in the transfer of appropriate data, information, and recipes is becoming an essential factor in support of technology transfer. The ability to narrowly focus on control limits with parameterized recipes in order to transfer a recipe to production is becoming more important with every product moving though the channel. The ability to link to electronic lab notebooks, PAT systems, MES, control layers, and business systems is crucial to taking technology transfers into a new and improved reality.

Summation

Conventional technology transfer procedures are challenged by errors and site-to-site inconsistencies as large volumes of information are transferred manually in paper or electronic document format. These problems can be reduced or eliminated since advanced technologies and tools are now available to improve these practices. Companies that embrace these capabilities will be able to bring products to market more quickly with consistent, well-characterized, quality processes.

Emerson Life Sciences consultants are available for in-depth discussions on ways to improve knowledge management and standardize on a common set of tools for successful, error-free technology transfer. For more information contact:

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