Pharmaceutical MANUFACTURING

SUPPLY CHAIN EXCELLENCE

Tech Transfer: Let's Take It from the Top

Why starting with a top-down approach to process definition and automation means better results at the bottom of the supply chain

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INVESTMENTS IN life sciences research are driving a significant uptick in the pipeline of new drug substance compounds. Rapid development of these new compounds into products drives a company's bottom line. But increasing global regulatory requirements coupled with competition from generics and biosimilars means that successful developments have less and less time as the exclusive offering — where pharmaceutical companies regain the bulk of the return on their development investment. Overcoming technology transfer challenges faced when moving product from lab to commercial manufacturing to the patient can help increase exclusivity time.

IMPROVING TECHNOLOGY TRANSFER

At the heart of making the research-to-production process more efficient and getting therapies to patients faster is a focus on improving technology transfer.

Because each stage of technology transfer is commonly handled independently with differing employees, processes, equipment, needs and locations, moving the product from one phase to the next can be cumbersome and inefficient.

To accelerate this pipeline and improve technology transfer effectiveness, four core conditions must be established:

- A corporate culture and associated operating environment that supports utilizing common drug manufacturing steps within and across pipeline phases
- Alignment of the standardized manufacturing and reporting steps to be used across each phase
- A clear pipeline management change control mechanism to pass the common manufacturing aspects to the next phase and to ensure that the current standards are used
- Clearly defined strategies for data collection, organization, comparison and analysis

Ideally, these four conditions will be addressed across all phases of a drug's development process before the earliest stages of research and development take place.

THE NEED FOR A STRUCTURED ENVIRONMENT

Though all stages of the development process are essential to the creation of a new product, different departments tend to be siloed from one another and focused on their own unique needs. Research operates independently of development/clinical, which is entirely separate from commercial manufacturing. With no organizational incentive to connect the production operations of these groups, moving the drug's manufacturing and packaging needs from one stage to the next becomes extremely inefficient.

Groups face significant complications with compatibility between recipe steps, utilized equipment, materials consumed and data collected during different phases. Key individuals involved in technology transfer must successfully hand over critical process parameters and quality attributes, equipment types and characteristics, all the recipe information (steps, sequence, materials, tests, etc.) and all the documented process understanding so that product development will progress successfully in later stages. Further complicating this process is that typically all the manufacturing technology to run production and capture data in each stage are different systems, designed by different manufacturers for different purposes, running the sequences differently and collecting data in different structures.

ORGANIZATIONS MUST FOCUS ON TOP-DOWN MANAGEMENT OF TECHNOLOGY **TRANSFER TO MITIGATE TIME LOST.**

If there is a problem with the product during clinical trials or manufacturing, the problem must be traced through multiple systems with multiple interfaces, without impacting the varied development or production work in progress.

IMPLEMENTING STRUCTURE

Organizations must provide meaningful cross-group

incentives and identify clear owners of their product lifecycle management business process. Executive management must lead the development and implementation of this change to both confirm the priority and to resolve conflicts and roadblocks. People driving technology transfer must clearly understand both their own department's needs as well as the needs of the next stage of development.

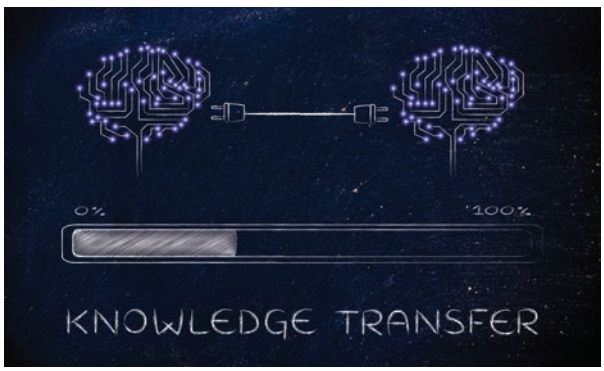
Some life sciences organizations have begun to approach technology solutions to this problem. Implementing individual systems geared toward department needs yet designed to work in other stages enables independent phases of the development structure to maintain and customize systems while still allowing for easy transfer, location and auditing across development. Integrated and scalable process control systems and manufacturing execution systems — such as Emerson's DeltaV distributed control system (DCS) and Syncade manufacturing execution system (MES) — facilitate efficient sharing of manufacturing procedures and data across the development chain. By working with an automation vendor early to define control systems and strategies, organizations can significantly simplify cross-departmental transfer.

STANDARDIZING TO IMPROVE EFFECTIVENESS

There are many benefits associated with utilizing standards for business processes and the associated technology supporting the execution of those business processes. Top examples include:

- Reduction of variation in work performance
- Reduction or elimination of errors and mistakes
- Improved, consistent quality
- Established scales and increased capacity for efficient task completion
- Visual management
- Seeing when processes are not operating normally
- Improved reporting, analytics and analysis practices

Establishing manufacturing standards across development stages presents challenges. How do you support the process flexibility and variability needed during development while also managing the enforced compliance required for commercial manufacturing? For example, maintaining common standards on recipes in each stage is critical to success. If critical process parameters require different names, sizing characteristics and testing methods between stages, the organization will waste valuable time and resources trying to reconcile this information to troubleshoot process problems and find a remedy. This problem gets compounded as all elements required to define a product manufacturing process (e.g. equipment, materials, recipe steps, etc.) are included.



STANDARDIZING SOLUTIONS

To ensure standardization, a key best practice is early collaboration between life sciences organizations and automation/IT suppliers to identify a structure for naming the pieces of the manufacturing process and building block objects to execute it. Production elements must always be defined consistently, with top-down direction, so that they can be transferred between stages reliably.

Each stage performs many similar tasks, but on a different scale. Research may be performing a task on a bench-scale bioreactor that manufacturing will complete in a 2,000-liter reactor, but the key elements between the processes are similar. Early engagement with automation and IT application experts can help decouple names, recipes and sequences from the equipment on which they are being performed. This allows scalability across the stages and provides the structure for transferring the process to the next stage.

Because organizations rarely purchase equipment all at once, it is often impossible to standardize all equipment. To account for operational differences, pharmaceutical organizations need to develop equipment class/instance standards that allow them to operate with a variety of equipment. Identifying critical quality attributes (CQA) and critical process parameters (CPP) from the earliest stages of research and development so that these key thresholds are clear is critical to decouple the specifics of the equipment from the production process. When CPPs and CQAs are clearly defined and updated throughout the development process, small differences between equipment can be understood and managed within the recipes quickly and easily.

Standardization can also have a significant impact on validation. The more bespoke solutions that are deployed, the more validation that's required. While there are usually no validation implications in the development lab, once the molecule moves to clinical and production, the level of validation required is directly related to how closely GAMP Category 4 versus Category 5 methods are followed. By using aligned, COTS packages, validation efforts can be reduced,

and validation documentation can be leveraged across the manufacturing areas.

THE CASE FOR CHANGE MANAGEMENT

Changes can occur at any stage of the development process. Whether during clinical trials or commercial manufacturing, it is essential to understand the impact of a change as well as enforce the change to maintain consistency across all systems and stages. Even small changes can have big impacts. If commercial manufacturing decides to make a cost saving change to save money on product vials, it is essential to know if there were any critical issues surrounding vial selection as well as the potential impact of having to re-validate all the product labeling. Without a high-quality change management mechanism in place, it can be difficult to identify the full impact as well as track down and consolidate any problems caused by making this vial change, much less avoid issues by predicting them.

TRACKING CHANGE THROUGH THE PIPELINE

Changes made to product development and production need to be made based on informed decisions and managed to meet regulatory requirements. Making informed decisions means having tools with fast access to data at every level and the ability to populate change data across all systems. Building blocks include a DCS and MES with change control and export/import features. Easy import/export of data between systems enables an embedded audit trail that can track and confirm changes as the basis for aggregating change records across multiple stages of the development process.

An additional layer of product lifecycle management (PLM) applications can manage what needs to be changed in each stage and facilitate using the import/export tools of the systems within a stage to ensure compliance. The PLM becomes a key tool for analyzing and communicating necessary changes.

MORE DATA, MORE PROBLEMS

As an organization expands its needs, the storage and organization of data become more fractured and the environment becomes more complex. As a product manufacturing process moves from stage to stage, different personnel will need to make comparisons. A researcher might be keeping copious lab notes, but if those notes are handed off as a large stack of handwritten log books covered in sticky notes, essential context won't transfer. Operators in later stages will be unable to make efficient use of the information.

Each level of the development process will have its own tools for storing data and being efficient, but what happens when that data needs to be recovered? Within each individual system there are good analytical tools, but those tools are often proprietary to the needs of the group controlling the data. This makes data analysis by another group a cumbersome and frustrating process.

Life sciences companies are drowning in data that is lacking context. Finding a way to efficiently analyze this data presents several obstacles. First, an individual must have access to the data. The analyst will also need to determine or develop context for the data once it has been accessed. Further complicating analysis is the need for proper analytical tools to make use of the data once it has been found and contextualized. Even in highly disorganized workspaces, these problems can be overcome, but the time and expense of creating a workaround is far too high for the modern pharmaceutical marketplace.

CORRALLING DATA

There isn't an easy and fast solution to the cumbersome task of data management. Organizations can invest in tools like artificial intelligence that will scrub and sort masses of data for easier use, but these tools are both costly and in their infancy. On the other hand, companies can develop systems to structure data properly from the very beginning, making it easier to collect and use, but this will only help with future data, not the trove of stored data that established companies will already have on hand.

The reality is that many organizations must embrace a combination of the two processes: cataloging old data where possible, and developing clear policies for structured, organized creation of future data. As regulations increase and margins tighten, life sciences companies will need to be nimbler in their handling of data to drive efficiency. The sooner companies start managing data the better, and the less data they will need to contextualize for future projects or when AI becomes a practical reality.

FINDING A WAY FORWARD

Bringing a product through the pipeline from research to market will always be a costly process. However, life sciences organizations are pushing themselves to resist the urge to throw their hands in the air and accept excessive costs and frustrating inefficiencies. To survive in the modern global pharmaceutical marketplace, organizations must focus on top-down management of technology transfer to mitigate time lost in production, quality, regulatory and supply-chain issues. When these organizations make the pipeline process more affordable, easier and faster, they have the potential to save millions, if not billions of dollars while providing more global access to life-enhancing products.

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