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The Four Pillars of Technology Transfer

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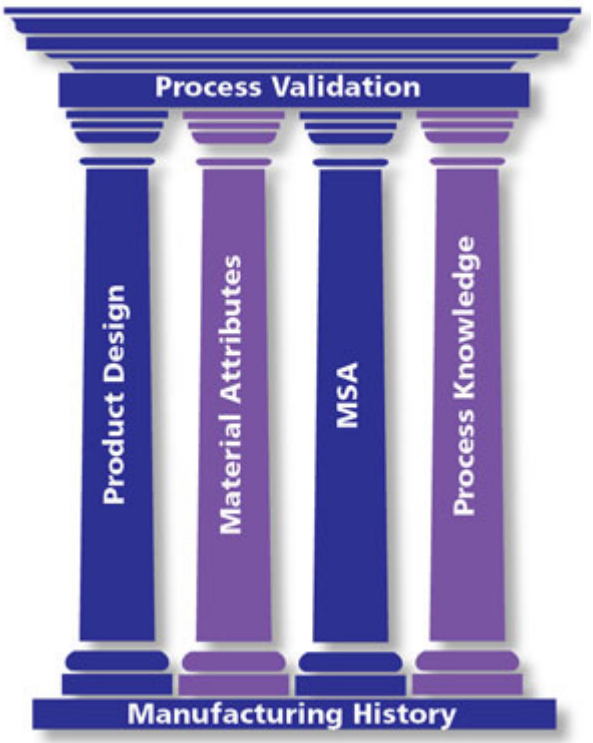
In today's marketplace there are very few business strategies that do not include technology transfer as part of the competitive landscape. Whether driven through consolidation, in/out-licensing or outsourcing, the ability to effectively transfer and commercialize a product can mean the difference between keeping or taking marketshare. Legacy products in particular represent significant technical challenges in technology transfer because historical development data may not be adequate to support the new Stage 1 process validation requirements and must be integrated as part of the technology transfer plan.

Technology transfer can take place at almost every step of the drug development lifecycle, from candidate molecule identification all the way through commercial manufacturing. Let's look at the basic steps involved in transferring an existing commercial product from one commercial site to another commercial manufacturing site.

The Four Pillars

To transfer an existing commercial process successfully, we break down the process into four basic elements, as shown in Figure 1, below.



These elements reflect the core foundation of understanding to demonstrate a successful technology transfer project and lay the groundwork for moving into process validation. Let's look at each of these elements in detail:

Product Design Understanding

It is reasonable to ask, why go back to the product design for a commercial product already on the market? The product design provides valuable insight in terms of process risk analysis and potential product performance hazards when transferring the process to another site. The loaded dose, drug release profile, functional excipients and analytical method capability are the basic parameters required to establish a control strategy. Legacy products in particular may not have much background information to rely upon and may require generating data as part of the tech transfer plan. Whether a product involves immediate, modified, or controlled release dictates the level of characterization required for demonstrating understanding in the new process. Applying a risk assessment tool to the process unit operations, intermediate and final specifications can be a very effective method for efficiently summarizing process understanding and available supportive data. This can then be used as a basis for developing the technology transfer plan. One element of the product design often taken for granted is the relationship between the immediate and final product release specifications and process predictability. Taking drug dissolution as an example, recognizing where the intermediate dissolution time points are on the dissolution curve, e.g. is the specification timepoint on an inflection point in the curve, can determine whether you must worry about true process variability or simply address the inherent variability of a poorly designed specification.

Material Attribute Understanding

Central to any process characterization exercise is the fundamental requirement to characterize and understand the role the drug substance and key functional excipients play in terms of process predictability and product performance. It is very helpful to know if a drug API has known polymorphs that could result in degradation of products or affect product potency and stability. Knowing where the melt and glass transition temperatures for the drug substance and key functional excipients can provide the framework for downstream confirmation studies. Basic data such as particle size distribution or functional measurements such as the Carr Index can be very helpful in driving down risk as characterization studies are created for the process being transferred. Fundamental understanding of the product performance as dictated by the processing of the drug substance can go a long way toward minimizing critical process parameters. This will have a huge long term advantage when it comes to developing the Stage 3 process monitoring plan required by the new process validation guidance.

Measurement System Analysis (MSA)

While it is often overlooked, it is very important to understand the resolution of the measurement tools being used to characterize the process. Often described as method Reproducibility and Repeatability and quantified using a Gauge R&R (GRR), this factor is often an impediment to true process understanding for legacy products. A GRR greater than 20 percent with less than 5 categories of distinction makes it very difficult to differentiate between measurement noise and true process variation. This can be a game

breaker when trying to establish acceptance criteria for the Stage 2 Process Performance Qualification (PPQ).

Process Understanding

This final element may seem obvious but the key to process understanding is being able to separate those process parameters that dictate process predictability and those that affect product performance. ICH Q8 focuses on the latter as does the new process validation guidance. Conducting characterization studies to define and provide process understanding of the process limits for the Normal Operating Range (NOR) and Proven Acceptable Range (PAR) is central to establishing a defensible final process validation strategy and to anticipate potential transfer problems. A well-designed characterization study ensures that true critical process parameters are defined prior to implementing the final control strategy.

Conclusion

Technology transfer requires a foundation in process and product understanding in order to minimize program risk. Understanding these four elements will establish a technical foundation that can be applied to establish an effective control strategy during the technology transfer program and lay the foundation for supporting process validation as defined in the FDA's new process validation guidance.