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TRANSLATING QBD GUIDANCE INTO DEVELOPMENT OBJECTIVES

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About The Author

A 25-year career in the pharmaceutical industry that is characterized by its breadth and extensive experience in all phases of drug development, from pre-clinical to post-marketing, with biologics and drugs. With hands-on experience in manufacturing process development, his expertise has been within CMC and Regulatory Sciences.

Ed has served as an advisor to emerging start-up and established pharmaceutical companies on the development of in-line and pipeline products and opportunities. Starting in process development and technology transfer at Lonza to his years with Pfizer, Inc. he managed submissions, as well as regulatory strategy for the development programs. After that, he was in drug regulatory affairs with numerous emerging biotech firms.

Today's new regulatory environment highlights innovative approaches to process development and manufacturing controls while forcing us to think about the practicalities of implementation. Unfortunately, broadly written FDA Guidances are subject to interpretation, thus making it difficult to confidently distinguish recommendations from actual requirements for any given phase of drug development.

The absence of clear guidance creates uncertainty regarding product development plans, potential misalignment of priorities, delays in the regulatory review of filings, and inconsistent standards from product to product and Sponsor to Sponsor. Proper application of the regulations (i.e., requirements versus recommendations) during preclinical through early-stage clinical development is now more vital than ever. This newsletter is designed to offer you practical suggestions for translating evolving regulatory guidance into coherent drug development goals that will meet FDA scrutiny.

Current FDA initiatives in Quality by Design (QbD) are based upon the concept of establishing product quality targets that evolve through the early and late stages of product development. The objective is to develop a sound scientific basis for manufacturing that accommodates a defined range of material and operational variance while maintaining quality

This increased focus on quality, however, requires both manufacturers and pharmaceutical sponsors to make larger investments in analytical methods and process development, well in advance of approved commercial operations. Practical implementation of Quality by Design principles needs to balance clinical and commercial risk with investments in CMC development programs. The following are 3 basic steps toward the practical implementation of QbD initiatives that are practical and useful in all phases of drug development.

Step 1. Product Characterization
Recognized reference standards rarely exist early in development, so an in-house primary reference, including product attributes such as structure, purity, chemical modifications, and biological potency, must be made and fully characterized.

Reference standards can be established prior to a finalized process or extensive knowledge of product stability. As soon as a process resembling that which will be used to generate clinical trial material is established, aliquots of representative reference material should be cataloged for use as a bridging standard.

Reference standards are essential for developing analytical methods to monitor performance over time. Tracking trends in specification and product attributes also complement stability data and ensure against product drift.

About DS Inpharmatics

DSI is a full-service CMC Drug Development and Regulatory Affairs consulting firm combining in-depth technical knowledge of product development with regulatory strategy and content authoring for all phases of the review and approval process in the U.S., Canada, and Europe.

Our group practice is composed of pharmaceutical scientists with decades of drug development experience in each subdiscipline of Chemistry, Manufacturing, and Controls. Whether your needs are comprehensive or tightly focused, DSI will help you keep your drug development program on track and under budget.

Not just advice. DSI provides you with flexible scientific resources to fill in-house expertise gaps and expanded operational capability to design and implement compliant drug development programs.

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Step 2. Process Characterization and In-Process Testing
Process characterization and the identification of critical product attributes should occur early in phase development. Once human trials progress into Phase 3, it becomes increasingly risky and difficult to make critical changes. Investing early in process characterization reduced the prospect of batch failure and provides supporting data to assess the impact of deviations and changes as they arise-without delaying the clinical program.

Quality by Design places emphasis on proactively designing product quality and control into the process through a better understanding of the underlying science and manufacturing process. Process optimization and careful design of experiments can help identify variances and produce data useful for defining the 'edge of failure'. This information provides a scientific basis for setting realistic limits around key process variables. Specifications are traditionally set without broad limits early in development, then narrowed as processes and the level of product understanding is refined.

Manufacturing process changes are inevitable during the course of development, whether for scale-up or for refinements aimed at improving commercial manufacture. When significant process changes are made, it is essential that methodologies be in place to demonstrate comparable product strength, stability, and above all safety (e.g., impurities and contaminants).

Step 3. Analytical Method Development and Stability
Ultimately, it is better to invest in early resources in the development and qualification of analytical methods that balance product function and safety with manufacturing capabilities than invalidating early methodologies which may end up being abandoned. It's not unusual for early methodologies to be replaced to facilitate larger-scale processes or tweaked (e.g., solvent changes to improve peal resolution).

Finally, both small molecules and biologics are susceptible to a number of environmental influences including temperature, pH, light, oxidation, ionic strength, chemical modification and drying. It is important to understand how different degradation and/or denaturation pathways affect the product. Once again, the earlier meaningful and reliable analytical methods are developed to characterize pathways of chemical and physical instability the better.

Accelerated stability and forced degradation studies can be used to acquire insight into product stability. Ideally, analytical method development should be integrated with the formulation development program for early identification of appropriate product attributes, as well as more traditional elements such as optimal storage conditions.

Stability-indicating assays focusing on product attributes that are critical to potency, activity, and safety should also be developed and qualified early. Stability-related changes can result in safety issues such as immunogenicity or unwanted side effects (e.g., toxicity from degradation products). Correlating forced degradation studies with genotoxicity, general toxicity, and/or immunogenicity experiments can identify product attributes associated with safety and asses the risk of degradants.

Know Your Product
There is simply no substitute for having a sound scientific understanding of your product and how it is produced. The more effort you put into building the appropriate methods and understanding the variability of the process, the better prepared you will be to make informed decisions and deal effectively with unanticipated problems.

Quality by Design initiatives aim to help control the quality of final products through process and product understanding, as well as incorporating better control through in-process analytics and knowledge of key variables.