

Achieving the “desired state”

Initiatives to adopt modern approaches for ensuring drug quality and establishing more-efficient manufacturing processes aim to achieve the “desired state” of pharmaceutical quality assessment. In this ideal situation, regulatory policies encourage continuous product improvement and innovation, and all parties understand the relationship between in-process controls and final product specifications. Moreover, a manufacturer that can meet higher quality standards through product control systems would benefit from greater regulatory flexibility.

Realizing this desired state of enhanced product quality and risk-based regulation requires a quality by design (QbD) approach. QbD involves basing product specifications on a mechanistic understanding of how product formulation and process factors affect product performance, as opposed to drug data empirically derived from test batches.

QbD covers product life cycle development from early target identification through establishing process parameters to postmarketing improvement. A manufacturer will start with interim specifications determined by the design of an appropriate process, but limited manufacturing experience. Early in the manufacturing process, controls are set for impurities and particle size, for example. Later, acceptance criteria are modified (loosened or tightened) as the manufacturer gains experience with the product and the process to reduce variability and revise attributes and in-process controls. The aim is to rely more on process control and in-process monitoring and testing, and reduce dependency on end-product testing.

An important goal of QbD is to use the process knowledge and understanding gained from pharmaceutical development to support real-time product release. This approach encourages the use of scientific methods and statistical tools to achieve continuous improvement in formulation and process. Under the desired state, specifications reflect the potential risk from variation in product quality and performance measures. The manufacturer establishes appropriate quality measures through dose ranging studies, clinical trial modeling, and biomarker data. Certain quality attributes will emerge as critical, although others may be useful primarily in ensuring that a manufacturing process is robust. More flexible acceptance criteria may be appropriate for those attributes that have less effect on the patient.

QbD must be built into product and manufacturing process designs to meet certain clinical performance measures. This process involves defining a product design space in which the manufacturer can use scientific approaches to establish appropriate process controls and specifications.