can have an adverse impact on manufacturing as well as quality characteristics of the finished product. The holding of the bulk quantity of the finished product before packaging may require special consideration for some products (e.g., orally disintegrating tablets and soft gel capsules). Appropriate hold studies should be conducted to demonstrate that holding the intermediates and in-process materials do not adversely impact downstream processing or product attributes. These studies should be conducted on drug, granulating and coating solutions, dry granulations, compressed tablets and capsules, and coated tablets before packaging. Some products may suffer physical damage if held in large quantities (drum or boxes) for several weeks under relatively high humidity or are transported in other facilities for packaging.

Formulation Design and Process Development Optimization

During early stages of product development, the qualitative and quantitative formulation composition is derived from laboratory-scale trials. The processing steps utilized to attain the desired performance characteristics of the dosage form are also identified. The work conducted during the formulation trial stage should reveal an understanding of the properties of active ingredient, excipients, and processing parameters that are critical to the intended quality attributes of the dosage form. At this stage, the development scientist should consider the design space to establish a range of process parameters and formulation attributes that consistently assure the quality of the product. The elements of QRM principles should be utilized when confirming the established ranges of formulation composition and processing parameters critical in achieving successful scale-up. This establishes an understanding of how the formulation and processing parameters influence product quality and performance in large-scale batches. A thorough understanding of the impact of manufacturing process on formulation components and the end product is achieved via implementing the Quality-by-Design (QbD) and DOEs as outlined below.

QbD in Generic Product Development

To improve efficiencies and modernize the pharmaceutical industry, in 2004, the US Food and Drug Administration (FDA) started a significant initiative titled "Pharmaceutical GMPs for the 21st Century: A Risk-Based Approach" [11]. An important part of this initiative was to shift the industry focus away from Quality-by-Testing to QbD, whereby drug development ensures enhanced understanding of the product and process. The International Conference on Harmonization (ICH) guidelines—ICH Q8: Pharmaceutical Development [12], ICH Q9: QRM [13], and ICH Q10: Pharmaceutical Quality Systems [14]—provide the abstract-level background on how QbD impacts and ensures drug product quality. The FDA's Office of Generic Drugs (OGD) has published several reports and presented at public industry forums, focusing and defining QbD specifically for generic product developers [15–17]. In addition, in 2007, the OGD implemented the question-based review for the CMC section of the Abbreviated New Drug Applications (ANDAs) [18]. This new process implemented several elements of QbD into the review process, including