INTRODUCTION

Development of oral pharmaceutical drug products presents many technical and regulatory challenges. Specifically, these include proper characterization of active pharmaceutical ingredients (API), assurance of compatibility of inactive ingredients with the active components over the shelf life of the product, processing, manufacturing, quality controls, and compliance with code of federal regulations and draft federal regulations under the Code of Federal Regulations (CFR) provisions for comments and approval process at the U.S. Food and Drug Administration (FDA).

Code of federal regulations mandate that any generic drug product intended for human use must be approved by the Agency for marketing a generic drug product and its multistrengths in the United States. These code of federal regulations provide assurances to the consumer that these generic drug products are safe, therapeutically equivalent, and effective in the same manner as the innovator or branded drug products approved previously as New Drug Applications (NDAs) by the FDA. Additionally, the quality-control information presented by a generic product manufacturer or sponsor in the Abbreviated New Drug Applications (ANDAs) documents the evidence that the API used in the dosage form—may it be a parenteral, oral solid dosage, topical, inhalation, implant, or a specialized delivery system form—is rigorously tested to comply with the regulatory mandates of acceptable limits of compendial or regulatory specifications mutually agreed upon by the sponsor and the Office of Generic Drugs (OGD) division of the FDA. The reader is referred to numerous Code of Federal Regulations and Guidance issues on this topic [1–8]. For the new millennium, the FDA has implemented the 21st-century pharmaceutical current good manufacturing practices (cGMP) initiative and quality-based design for new drug product approval of the innovator (brand) company. The OGD in the FDA has developed a questions-based review system for the generic company to implement a questions-based development (QbD) program in development and manufacturing of generic products and to assess generic product sponsors' QbD in their ANDA filings.

Method Development and Its Importance

Method development in the generic product design phase (which is intended to define the target product quality attributes profile) begins with full analytical testing and reproducible characterization of the API for which there is a Drug Master File (DMF) registered with the Agency. It is becoming imperative to apply QbD principles for method development. The DMF submitted to the FDA by the API manufacturer contains confidential details of the synthetic process, drug substance form, and purity, along with identity of impurities listed in the API specifications and their pathways of formation. An active partnership between the API vendor and ANDA sponsor who is developing the finished dosage form is essential to assure that the API meets the cGMP requirements for testing and stability with adequate control on the manufacturing process. In case any deficiency is observed by OGD, the API vendor has to address their response to the deficiency related to the API before the ANDA sponsor can address their response for the deficiency related to the chemistry, manufacturing, and control (Chemistry, Manufacturing, and Controls section of ANDA) of the finished dosage form.