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RESEARCH ARTICLE

Impact of Quality by Design in Process Development on the Analytical Control Strategy for a Small-Molecule Drug Substance

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Abstract Development of the arzoxifene hydrochloride drug substance manufacturing process, first via a traditional approach and subsequently via an enhanced approach, provides an informative case study in quality by design (QbD). The primary focus of this paper is to illustrate the impact and advantages of QbD on the impurity control strategy. By operating the process at the extremes during design space studies, a larger collection of organic impurities and higher levels of typical impurities are observed in the intermediates. This enables a more thorough understanding of the ability of the process to purify the drug substance and results in a more complete and robust set of intermediate specifications as well as broader and more robust analytical methods. We demonstrate that, when each of the synthetic steps are operated within the design space, the byproduct impurities in the intermediates will not exceed levels found to be rejected in subsequent steps, ensuring that the drug substance will meet its critical quality attributes. Through the rigorous application of an enhanced process development approach, we have designed quality into the arzoxifene hydrochloride drug substance. As a result, real-time release of the intermediate batches is proposed to increase the process throughput and avoid the expense of nonvalue-added testing.

Keywords Arzoxifene hydrochloride · Quality by design (QbD) · Critical quality attribute (CQA) · Enhanced process development approach · Impurity control strategy · Real-time release (RTR)

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Introduction

Arzoxifene

Arzoxifene hydrochloride is a selective estrogren receptor modulator (SERM) which was under development for the treatment of osteoporosis and reduction of the risk of breast cancer for postmenopausal women [1]. The route of administration was an oral daily dose of 20 mg tablet. At the end of the phase III clinical trial, the decision was made not to submit the compound for regulatory approval [2]. While arzoxifene met the primary endpoint of the phase III trial, which was significant reduction of the risk of vertebral fracture and invasive breast cancer in postmenopausal women, there was no statistically significant difference from placebo in key secondary endpoints (nonvertebral fractures, clinical vertebral fractures, cardiovascular events, and cognitive function). Adverse events included venous thromboembolic events, hot flushes, and gyenecological events, more frequent than placebo. At the time of project termination, a final draft of the common technical document (CTD) had been completed. The draft regulatory submission included full implementation of a quality by design (QbD) approach for both the drug substance and drug product manufacturing processes. The focus of this paper will be the application of QbD to the drug substance.

Control Strategy

Impurities in a drug substance arise from multiple sources (see Table 1). They may arise from impurities in starting materials that either carry forward unreacted or are chemically transformed to new impurities. Impurities may form as byproducts during intermediate processing. These impurities may be either well-rejected during intermediate isolation and washing, they may be partially rejected, or not rejected.