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CASE REPORT

The Application of Science- and Risk-Based Concepts to Drug Substance Stability Strategies

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Abstract The International Conference on Harmonization (ICH) has provided practical guidance on the amount and type of drug substance stability data needed to support marketing applications (International Conference on Harmonization 2001, 2002, 2003a, b). Additional guidance has been issued by the World Health Organization (WHO 2009). Recent scientific advances and practices have resulted in improved scientific understanding of the chemical and physical attributes that contribute directly or indirectly to drug substance stability. Combining this improved understanding with the science- and risk-based approaches detailed in ICH Q8, Q9, and Q10 allows for alternative and more scientifically driven approaches to meet the scientific and regulatory objectives for drug substance stability (International Conference on Harmonization 2005, 2008, 2009). In this paper, proposals are presented to more fully leverage enhanced product knowledge to design improved stability strategies. The chemical and physical attributes that potentially impact drug substance stability are discussed, and strategies that leverage accelerated stability studies are presented.

Keywords Stability · Drug substance · Stability-related quality attributes · Control strategy

Some of these concepts were presented at the AAPS Current Trends in Stability Workshop (Washington, D.C., September 2009): Colgan S. "The Application of Quality by Design's Science and Risk Based Concepts to API Stability Strategies"

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Introduction

The International Conference on Harmonization (ICH) Q8 states that pharmaceutical development should include, at a minimum, a definition of the quality target product profile as it relates to quality, safety, and efficacy, considering stability and several other factors. Q8 also states that a greater product understanding can create a basis for more flexible regulatory approaches, the degree of which is predicated on the level of relevant scientific knowledge. Although Q8 covers drug products, its principles can be applied to drug substance as well. ICH Q11 recently issued at stage 4 states that drug substance critical quality attributes typically include those properties or characteristics that affect identity, purity, biological activity, and stability. In addition, changes to the manufacturing process should be evaluated for impact on the quality of the drug substance. The evaluation should be based on scientific understanding of the manufacturing process and should determine appropriate process point(s) and testing to analyze the impact of the proposed change.

In regulatory filings, formal stability studies are designed to evaluate quality over time under the influence of temperature, humidity, and light and to facilitate the establishment of appropriate controls, retest periods, and underwrites packaging and storage recommendations. Drug substance stability is related to inherent properties of the specific compound, as well as its stability-related quality attributes. A stability-related quality attribute (typically a subset of quality attributes) directly or indirectly impacts stability but may or may not impact other considerations (such as manufacture of the drug product). Identification, quantification, and control of the stability-related quality attributes ensure drug substance quality over time.

There are potential benefits for the pharmaceutical industry, global regulators, and patients that could be realized by adapting scientific stability strategies that leverage understanding of