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CASE REPORT

Best Practices for Drug Substance Stress and Stability Studies During Early-Stage Development Part I—Conducting Drug Substance Solid Stress to Support Phase Ia Clinical Trials

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Abstract Regulatory guidances for drug stability testing during early development stages lack specifics. Consequently, companies either conduct more stability studies than necessary just to avoid regulatory questions or perform insufficient stability work resulting in regulatory questions and delays in drug development. Hence, there exist a pressing need and a great opportunity for pharmaceutical companies to share drug stability testing practices, rationales, and regulatory experiences for the early stages of development. This paper describes a quick, streamlined solid stress practice to support drug development from pre-clinical to Phase Ia Clinical Trials. By subjecting a few grams of drug substance to high temperature and high humidity (e.g., 70 °C/75 % RH, in open and closed containers, for three weeks) and to the ICH Q1B confirmatory photostability testing condition, the initial DS retest period and the initial shelf life of powder for oral solution can be reliably extrapolated, and a bulk packaging choice is made. In addition, the solid stress results can be used for multifaceted purposes. The solid stress practice offers a quick turnaround in obtaining adequate stability information for new drug development and achieves an optimum balance between risk and cost for Phase Ia clinical development.

Keywords Drug substance · Powder for oral solution · Early stage development · Solid stress · High temperature/high humidity · Photostability · Retest period · Shelf life

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Abbreviations

AC	Accelerated storage condition (e.g., 40 °C/75 % RH)
DS	Drug substance
DP	Drug product
HT/HH	High temperature and high humidity (e.g., 70 °C/75 % RH)
ICH	International Conference on Harmonisation
GLP	Good laboratory practice
GMP	Good manufacturing practice
LT	Long-term storage condition, e.g., 25 °C/60 % RH
LT/AC	Long-term storage condition/accelerated storage condition (25 °C/60 % RH/40 °C/75 % RH)
PFOS	Powder for oral solution
RH	Relative humidity

Introduction

Understanding and establishing the stability of drug substance (DS) and drug product (DP) is a very important drug development task. First, the knowledge of the intrinsic stability and degradation pathways of a new DS and a DP is essential for analytical methods development and validation, process development, formulation development, manufacture, packaging, storage conditions, and transportation needs. Second, establishing DS and DP stability is a regulatory expectation to ensure product quality, which may affect product safety and efficacy. To ensure product safety in all stages of clinical development, it is important that degradation products are quantitated and structurally identified when exceeding the International Conference on Harmonisation (ICH) Q3A identification threshold. Toxicological qualification and risk can then be evaluated, including in silico assessment of chemical