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RESEARCH ARTICLE

Best Practices for Drug Substance Stress and Stability Studies During Early Stage Development. Part III—How to Make Science- and Risk-based Stability Testing Decisions for Drug Substance Batches Produced after Manufacturing Process Changes

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Abstract During phase 1 and phase 2 drug development (early stage drug development), it is normal to continuously improve a manufacturing process, with changes made to the synthetic pathway, reagents, reaction conditions, crystallization parameters, drying conditions, or manufacturing equipment or scale or site. These manufacturing process changes ("process changes" used thereafter) may or may not affect quality attributes such as impurities, and quality attribute changes may or may not affect drug substance (DS) stability. But a common misconception is that almost all process changes and/or quality attribute changes affect DS stability, and a new (or repeat) stability study is conducted for the DS batch produced after process changes. This misconception is clearly refuted by our many years of DS stability experience. To understand how process changes might affect DS stability, we compiled and analyzed manufacturing processes, quality test results, and stability data for 48 batches from seven drug substances in recent development. Of these 48 batches, the seven first DS clinical batches were used as references against which the other respective 41 batches, which were produced after process changes, were compared for changes in manufacturing processes, quality test results, and stability data. This comparison showed that the chemical and physical stability of 36 (of the 41) batches was not affected by process changes, and the chemical or physical stability of the other 5 batches was affected by residual inorganic impurities, significant amounts of water or residual solvents, or significant changes in DS particle size distribution or surface area. These quality attributes that affect stability are called stability-related quality attributes (SRQAs). A new (or repeat) stability study is warranted only if process changes significantly affect SRQAs. We have established a procedure to systematically assess changes in manufacturing process and quality attributes (particularly impurity profiles), to identify SRQAs (risk assessment), and to make science- and risk-based stability testing decisions on whether and how stability testing for new DS batches should be conducted (risk management).

Keywords Drug substance · Manufacturing process · Process changes · Quality attributes · Impurity profile · Risk assessment · Risk management · Stability-related quality attribute (SRQAs) · Solid stress testing · Long-term and accelerated stability testing

Abbreviations

AC	Accelerated Storage Condition (e.g., 40 °C/75 % RH)
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (German Health Authority)
DS (API)	Drug Substance (or Active Pharmaceutical Ingredient)
HT/HH	High Temperature and High Humidity (e.g., 70 °C/75 % RH)
EMA	European Medicines Agency
GMP	Good Manufacturing Practice

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