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PERSPECTIVE

Verification of Design Spaces Developed at Subscale

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Abstract Recent concerns about the applicability of design space boundaries developed on small scale to commercial manufacturing processes have been raised by regulators worldwide. These concerns center around the scalability of unit operations and their corresponding process parameters, and the impact this has on the desired attributes of the drug substance or product. Requests have been made to verify design space boundaries with data generated at commercial scale. Because it is not always feasible to manufacture large-scale batches, alternative approaches to verification are necessary. The following article discusses various science-based strategies that could be used to verify design space boundaries. These approaches balance the requirements to address regulatory concerns and ensure that quality standards are maintained for both drug substances and products, within the operating constraints currently facing the pharmaceutical industry.

Keywords Design space verification · Quality by design · Process parameters · Quality attributes · Scale dependency · Modeling

Background

The information used to define design spaces is often generated at much smaller scale compared to the commercial batch size. Statistically designed experiments (DOEs), empirical/mechanistic models, univariate experiments, and prior knowledge are used during the development of manufacturing processes for drug substances and products. A comprehensive understanding of multivariate interactions between process parameters is expected, including the scalability of the design space which often occurs over magnitudes greater than ten times. ICH Q8(R2) Pharmaceutical

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