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RESEARCH ARTICLE

Development of a Design Space for a Unit Operation: Illustration Using Compression-Mix Blending Process for the Manufacture of a Tablet Dosage Form

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Abstract This paper describes the development of an orthogonal design space for a compression-mix blending unit operation for the manufacture of tablet dosage form using an empirical approach. Potential critical process parameters identified through a risk assessment process were assessed through a full-factorial design of experiment for impact on material attributes and drug product critical quality attributes (DP CQA). The impact on each individual attribute measured as responses were subjected to statistical analysis by analysis of variance and regression models were built on the statistically significant effects ($p<0.05$). Design space for relevant DP CQA was created using 95% predicted interval estimates. Orthogonal design space for the unit operation was proposed by overlaying design spaces generated for individual DP CQAs. The resulting orthogonal design space made implementation of manufacturing flexibility in to routine manufacturing process and into control strategy simpler and straightforward.

Keywords Quality by design (QbD) · Design space · Drug product CQA · Predicted interval · Design of experiments

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Introduction

The concept of "design space" to control quality and provide manufacturing flexibility is at the heart of QbD. ICH Q8 defines design space as "the multidimensional combination and interaction of input variables and process parameters that have been demonstrated to provide assurance of quality" [1]. As further clarified in ICH Q8 R(2)—an annex to *ICH Q8*, a design space can be "defined in terms of ranges of input variables or parameters, or through more complex mathematical relationships, defined as a time-dependent function (e.g., temperature and pressure cycle of a lyophilization cycle), or as a combination of variables such as principal components of a multivariate model. Scaling factors can also be included if the design space is intended to span multiple operational scales. Analysis of historical data can provide the basis for establishing a design space." Regardless of how a design space is developed, it is expected that operation within the design space will result in a product meeting the defined quality attributes [2].

The development and implementation of a design space is important as it can provide greater process understanding and can support regulatory and/or manufacturing flexibility. As described in ICH Q8 R(2), design space can be specific to a unit operation or span multiple unit operations. Establishing a separate design space for each unit operation is simpler and easier to achieve compared to a design space that spans the entire manufacturing process. So, one should take into consideration benefit of resource requirements and project timelines when developing a design space. For product life cycle management, developing a design space can be considered a dynamic process, so it continues to evolve as