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CASE REPORT

Model-Guided Design Space Development for a Drug Substance Manufacturing Process

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Abstract This case study outlines an application of quality by design principles to a drug substance manufacturing process. A hybrid process chemistry model consisting of mechanistic and empirical components was developed to guide the selection and verification of a design space. A multistaged experimental plan was employed to address specific goals at each stage of model development and design space selection. In addition to the multivariate evaluation of process parameters, accounting for the quality attributes of input materials was shown to be an important consideration when choosing a design space. The merits of a model-guided approach to selecting an invariant, experimentally verified design space (as opposed to a fully model-defined dynamic design space) are discussed.

Keywords Quality by design (QbD) · Design space · Active pharmaceutical ingredient (API) · Drug Substance Manufacturing process · Hybrid process chemistry model

Introduction

This case study presents an approach to design space development for drug substance production to support commercial manufacturing and a regulatory filing consistent with the quality by design (QbD) paradigm. In general terms, implementation of the QbD framework involves definition of critical quality attributes (CQAs), determination of specification limits, risk assessment of factors that influence the CQAs, evaluation of multivariate interactions, and design space selection and verification [1–4]. The philosophical underpinnings of QbD are well described in the International Conference on Harmonisation (ICH) guidances [5–7], and the application of these principles to drug substance process development has been described in the literature [8–10]. Distinguishing features of the current contribution include (1) the use of sequentially executed experimental designs to facilitate both mechanistic modeling and multivariate evaluation of factors (encompassing process parameters and quality attributes of input materials) and (2) consideration of business drivers when choosing a strategy for design space definition and verification.

As ICH Q8(R2) states: "The design and conduct of pharmaceutical development studies should be consistent with their intended scientific purpose. It should be recognized that the level of knowledge gained, and not the volume of data, provides the basis for science-based submissions and their regulatory evaluation." This study illustrates how a multistaged experimental plan can efficiently address the requirements of model development and design space selection.

An important outcome of this investigation is a model that can predict key impurity levels throughout a multidimensional parameter space. Recently, two approaches to the use of such predictive models within the context of a broader QbD strategy have been discussed in the literature. A predictive model may be employed to determine a distinct design space for each production batch (as in Castagnoli et al. [9]), or it may be used to guide the selection of a single design space, applicable to all production batches and defined by invariant parameter ranges (as in Hallow et al. [10]). Each approach has its

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