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CASE REPORT

# An Example of Utilizing Mechanistic and Empirical Modeling in Quality by Design

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**Abstract** In this case study, we present an approach for employing modeling to help define the design space for a reaction with potential to generate an impurity that could impact the quality of an API. Our approach broadly consisted of (1) evaluating the reaction parameters that can affect the critical impurity level to develop appropriate assumptions for a mechanistic model, (2) developing and evaluating a mechanistic model to predict the formation of the critical impurity, (3) defining a design space based on the model output to reduce in practice the acceptable parameter space to a practical number of parameters, and (4) verifying the design space through experimental testing. This work resulted in a verified design space that can be practically employed and includes wide parameters ranges for manufacturing flexibility.

**Keywords** Quality by Design · Design space · Mechanistic modeling · Empirical modeling · Verification

## Introduction

As an industry and regulatory led initiative, Quality by Design (QbD) aims to improve the quality assurance of pharmaceuticals, the efficiency of process development, and the performance of manufacturing through an investment in science, technology, and risk management. As an additional benefit of this approach, lower costs, and flexible regulatory approaches may be realized by participating firms [1]. Pharmaceutical development by a QbD approach has specifically placed emphasis on increasing scientific understanding of the manufacturing process, identifying sources of variability, utilizing sound risk management, and developing appropriate control strategies [2]. QbD intends to shift the focus of pharmaceutical manufacturing from quality control through product and input testing to quality assurance by increased process knowledge and risk-based process design. As the International Conference of Harmonisation (ICH) Q8 (R2) guideline states, "quality cannot be tested into products; i.e., quality should be built in by design" [3]. The principal elements of QbD include development of a risk assessment, design space, and control strategy [4].

The ICH Q8 (R2) guideline defines a design space as "the interaction of process inputs (e.g., material attributes, process parameters) that reliably deliver product of the desired quality" [3]. The design space may be established through the aid of design of experiments (DoE) [5], mechanistic models (e.g., reaction kinetic models), or mathematical models (e.g., principal component analysis) [6]. These methods provide knowledge about the interaction of parameters that can be used to define the process parameter design space, in contrast to the traditional method of establishing proven acceptable ranges through univariate experiments. Although conceptually simple, the definition of a design space can be quite challenging when considering the high dimensionality of the potential parameter space across multiple unit operations and often over several synthetic steps. In addition, assessing the suitability of models and determining an appropriate design space from model outputs can be equally challenging and is

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