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RESEARCH ARTICLE

# Adaptive Design Space as an Integrated Component of Quality by Design

**Benoît Igne · Zhenqi Shi · Sameer Talwar · James K. Drennen III · Carl A. Anderson**

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**Abstract**
*Introduction* The US Food and Drug Administration requires pharmaceutical companies to develop extensive process understanding prior to routine manufacturing of drug products. Through development and validation, drug manufacturers enhance their process understanding and identify an acceptable range of process parameters for each unit operation; this is referred to as the design space. Typically, limited work is done to study the effect of long-term raw material variations on the robustness of the design space. In the present study, the development of a design space for a tablet formulation containing two APIs (acetaminophen, caffeine) through a direct compression process was investigated.
*Material and Methods* A design of experiment including different excipient ratios of microcrystalline cellulose and lactose, two croscarmellose sodium levels, four tablet compression forces, and four blend parameters was created using an industrial-size press to define a knowledge space. Quality attributes (disintegration time, dissolution, radial tensile strength, and friability) were measured and a design space derived. In order to test the robustness of the design space, raw material properties, specifically particle size of acetaminophen and ratio of lactose anhydrous to monohydrate, were modified. Also, compression parameters were varied.
*Results* Tablets were analyzed for relevant critical quality attributes (CQAs) to investigate how variability in raw materials can change the design space. The modification of the process parameters was used as a means of compensating for raw material variability to produce tablets that met CQA requirements. An adaptive design space approach based on the adaptation of critical process parameters is proposed to facilitate the creation of tablets meeting specifications despite variation in raw material properties.

**Keywords** Quality by design · Knowledge space · Design space · Adaptive design space · Raw material variability

B. Igne · J. K. Drennen III · C. A. Anderson (✉)
School of Pharmacy, Duquesne University
Duquesne Center for Pharmaceutical Technology,
600 Forbes Avenue,
Pittsburgh, PA 15282, USA
e-mail: andersonca@duq.edu

Z. Shi · S. Talwar · J. K. Drennen III · C. A. Anderson
Graduate School of Pharmaceutical Sciences,
Duquesne University,
600 Forbes Avenue,
Pittsburgh, PA 15282, USA

## Introduction

Pharmaceutical Quality by Design (QbD) is a "systemic approach to pharmaceutical development that begins with predefined objectives and emphases product and processes understanding and process control" [1]. It consists of understanding the impact of formulation and manufacturing on product critical characteristics and identifying all sources of variability to implement a flexible and robust process that can adapt and produce a consistent product over time. This stands in stark contrast to quality by testing, where only the final product characteristics are considered. The goal of QbD is to utilize clinical relevance to determine product characteristics. In addition, under the QbD paradigm, batches may not be actually tested against specifications as the process understanding and process control provide sufficient evidence that a given batch will meet the specifications if tested [1].

The implementation of a QbD system involves the investigation of all the factors that can impact the critical quality attributes (clinical performance) of a drug product. It entails studying the effect of excipient and drug substance variability, exploring the impact of process parameters and the determination of the critical process parameters (CPP) and finally the development of a design space in the presence of interacting CPPs [2]. The International Conference on Harmonization tripartite guideline on pharmaceutical development Q8(R2) defines design space as "the multidimensional