J Pharm Innov (2011) 6:61–68
DOI 10.1007/s12247-011-9101-y

PERSPECTIVE

Application of Quality by Design Principles to Legacy Drug Products

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Published online: 10 May 2011

Abstract The concept of Quality by Design (QbD) is of paramount importance in designing and developing reproducible and robust drug products, processes and analytical methods, thus enabling regulatory compliance and ensuring manufacturability. Risk assessment, design space, and control strategy constitute the key elements of the QbD framework. In this paper, a data-based approach to developing robust pharmaceutical processes is presented and illustrated with an application to a drug product during a site transfer process. The key objective in applying QbD principles is to ensure that the product is designed and manufactured to consistently meet quality requirements. The approach presented simultaneously considers the variability in raw materials, quality critical process parameters and critical quality attributes. By nature, large historical databases of raw material (active ingredients and excipients) and process data exists for legacy products. Multivariate statistical models were employed to extract knowledge on critical variables. Furthermore, a number of design of experiments (DOE) were performed in the joint space of the raw materials and the manipulated process variables to develop the design space and control strategy with feedback control. The result was a joint space that combines the interaction of all the input variables such as raw materials and process parameters that have been proven to provide high quality. Throughout this paper, the use of multivariate statistical analysis and DOE and how they are applied to define meaningful raw materials specification and design space to achieve QbD are discussed.

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Keywords Quality by design · Design space · Control strategy · Multivariate statistical modeling · Optimization · Partial least squares · Feedback control

Introduction

Quality by design (QbD) is a systematic, science-based approach to pharmaceutical manufacturing that was defined in the International Conference on Harmonization Q8 guideline in 2005 [1]. Expectations were laid down that QbD will ultimately become a regulatory expectation and prerequisite for drug approval. In a sense, QbD represents a paradigm shift in applying more systematic methodologies with a focus on end-product quality. The premise of QbD then implies that the manufacturing process should be designed to meet the desired quality attributes, hence enforcing the concept of "design" of product quality versus "testing" of product quality. Although testing the quality has to remain an essential element of quality control, testing is conducted as a verification of the product quality.

In a QbD framework, one's goals should be to design processes that are insensitive or "robust" to disturbances. Thus, in the development and optimization of pharmaceutical processes, it is essential to ensure that the design will be able to satisfy product critical quality attributes (CQAs) despite raw material variability and other disturbances that may occur during operations. For instance, in manufacturing operations, it is quite common that the quality of raw materials varies during operation or that an alternate material or excipient has to be processed. Other sources of variations that often occur during process operation include ambient temperature and humidity variations, fouling of heat exchangers, and deterioration of mechanical equipment.