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CASE REPORT

Overcoming Inherent Limits to Pharmaceutical Manufacturing Quality Performance with QbD (Quality by Design)

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Abstract Pharmaceutical development and manufacturing systems typically rely on a Quality by Testing (QbT) model that use release testing and other measures to ensure product quality. However, there is a significant gap between typical pharmaceutical production system capability and supplied quality. To sustain high levels of product supply quality, the industry incurs a high cost of quality and retains value at risk. This paper presents research results from a systems engineering perspective using case study data that quantitatively evaluates the gap between pharmaceutical production system sigma and supplied quality. It also identifies the extent to which emerging Quality by Design (QbD) eliminates system contradictions that prohibit higher production system sigma performance.

Keywords QbD · Quality by design · TRIZ · S-curves · Technological evolution · Systems engineering

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Introduction

There is a significant gap between the level of quality of pharmaceuticals the industry supplies to consumers and the process capability of production systems. Migliaccio referenced the problem as "six-sigma products on the market with three-sigma processes [1–3]." Dean referred to this as the "Migliaccio Conjecture [2]."

Currently, most pharmaceutical development and manufacturing systems rely on a Quality by Testing (QbT) model to ensure product quality. To maintain high levels of product supply quality, the industry incurs a high cost of quality while continuing to sustain value at risk. (*Value at risk* refers to the inherent business risks that remain with the QbT model, such as recalls, loss of confidence, compliance findings, legal costs, etc.)

Design for Six Sigma literature has identified sigma walls or fundamental limits at which continuous improvement (CI) efforts (such as Six Sigma) reach diminishing returns. That is, without adequately designing for quality, processes hit a sigma quality wall before reaching six sigma even with the application of CI efforts.

As a potential solution, Quality by Design (QbD) is emerging in the industry to enhance the assurance of safe, effective drug supply to the consumer while improving manufacturing quality performance. The goal of the research presented in this paper is to quantitatively evaluate the gap between pharmaceutical production system sigma and supplied quality from a systems engineering perspective, and identify the extent to which emerging QbD eliminates system contradictions that limit higher performance. The goal of the paper is also to offer additional rationalization for QbD.

The research includes four hypotheses, which are (1) the conjecture is true in principle (there is a significant gap between shipped quality and production sigma), (2) a reason