



# The future of pharmaceutical quality and the path to get there

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## ARTICLE INFO

### Article history:

Received 11 March 2017

Received in revised form 3 June 2017

Accepted 12 June 2017

Available online 12 June 2017

### Keywords:

Pharmaceutical quality

Six sigma

Quality by Design

Performance-based regulation

Advanced pharmaceutical manufacturing

Process capability

## ABSTRACT

While six sigma quality has long been achieved in other industries, it is rarely seen in the pharmaceutical sector. However, consumers and patients deserve six sigma quality pharmaceuticals with minimal risks of shortages or recalls. We propose that the future of pharmaceutical quality is six sigma, meaning that no more than 3.4 defects occur per million opportunities. We discuss the path to get there, including economic drivers, performance-based regulation, Quality by Design, advanced manufacturing technologies, and continuous improvement and operational excellence. This article outlines an ambitious goal and is intended to be thought-provoking in spite of the challenging path to get there. This goal is envisioned because it is in the best interest of patients and consumers and is realizable with continued advances and investments in science and technology. The fundamental destination of pharmaceutical quality has been long envisioned: *a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight.*

Published by Elsevier B.V.

## 1. Introduction

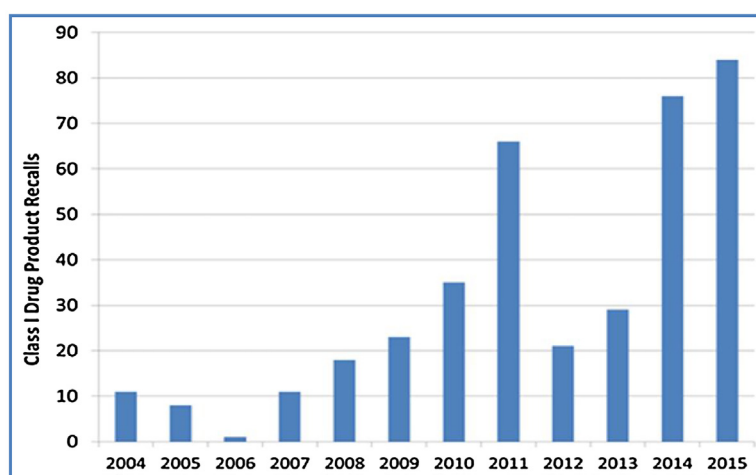
The U.S. Food and Drug Administration (FDA) Pharmaceutical Quality for the 21 st Century Initiative aims to promote *a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight* (FDA, 2004a). Over the years, substantial progress has been made toward this vision, including process analytical technology (PAT) (FDA, 2004b), Current Good Manufacturing Practices (CGMPs) for the 21 st century (FDA, 2004a), Quality by Design (QbD) (FDA, 2009a), and Emerging Technology (FDA, 2015a) initiatives. Overall product/process understanding and manufacturing quality have improved in the industry as a whole. While the quality of newly introduced products has been significantly higher, concerns over pharmaceutical product quality have continued due to unacceptably high product recalls and drug shortages. Largely driven by legacy products, the number of product recalls has actually increased over recent years (FDA, 2015b) (Fig. 1). Alarming drug shortages have also persisted as product quality remains a primary driver (ISPE, 2017). The drive to improve quality and address shortages and recalls is motivated by the patient and consumer. These recent trends serve as a reminder

that we still have a long way to go in improving quality in the pharmaceutical industry to better serve these patients and consumers.

Therefore, to realize the FDA's vision for the pharmaceutical manufacturing sector, we must continue to improve the overall quality of pharmaceuticals. Manufacturing capability in many diverse industries is analyzed using sigma, the number of standard deviations between the process mean and the nearest specification limit (Nunnally and McConnell, 2007). We propose that the future of pharmaceutical quality is six sigma, meaning that no more than 3.4 defects occur per million opportunities. This is a dramatic improvement from the current two to three sigma quality seen in pharmaceutical manufacturing. Two sigma quality represents 308,537 defects per million opportunities. The six sigma vision of the future of pharmaceutical quality requires the reduction of defects from ~30% to 0.0003%. While six sigma has long been the target for quality in the electronic, communication, and automobile industries (Harry and Schroeder, 2005), it is rarely seen in the pharmaceutical industry where six sigma quality is, in many cases, far from reality. However, consumers and patients deserve six sigma quality products with minimal risks of shortages or recalls. Here we discuss the path to achieve six sigma quality for pharmaceuticals, including economic drivers, performance-based regulation, QbD, advanced manufacturing technologies, and continuous improvement and operational excellence.

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**Fig. 1.** Number of Class I Drug Product recalls per year (FDA, 2015b). A Class I recall denotes a situation in which there is a reasonable probability that the use of, or exposure to, the violative product will cause serious adverse health consequences or death. Recalls for misbranding (i.e. product marketed without an approved NDA/ANDA) were removed from the data set to focus on recalls initiated due to quality issues.

## 2. Economic drivers

The pharmaceutical industry is highly regulated because patients and consumers are generally unable to discern quality problems unless they cause severe adverse events or death. Public perception is that all products approved by the FDA are safe and effective. The public also expects approved products to be of equally high quality. Unlike electronics or automobiles, patients and consumers do not typically distinguish quality in the manufacture of pharmaceuticals. They expect every drug to have the requisite quality to address their medical condition regardless of how or by whom the drug was manufactured. Consequently, manufacturers have little economic incentive to leverage quality. It is easier to simply comply with FDA requirements. Woodcock and Wosinska (Woodcock and Wosinska, 2013) used economic theory to frame the drug-shortage problem as the inability of the market to observe and reward quality. Moving forward, we need to introduce incentives to the drug industry that enable the market to recognize and reward quality.

This lack of reward for quality reinforces price competition and encourages manufacturers to minimize costs. As a result, low cost manufacturers can maintain a market share based largely on price competition. Although not always the case, these manufacturers have high vulnerability to product quality issues, including product recalls and supply disruption. For many consumer products, recalls and supply disruption cause some inconvenience to the consumer and economic loss to the manufacturer. For pharmaceuticals, recalls and supply disruption can be life threatening, in addition to causing economic loss. Therefore, we believe quality drugs are a must, with reliability and sustainability taken into consideration.

A high quality drug product is defined as a product free of contamination that reproducibly delivers the therapeutic benefit

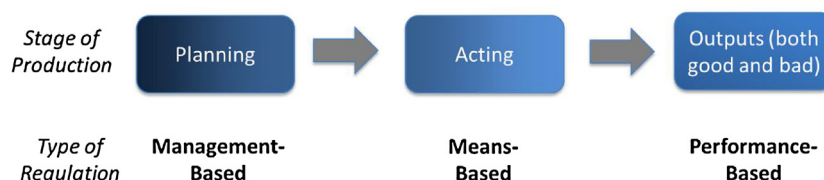
promised in the label to the consumer (Woodcock, 2004). Product quality is therefore fundamentally linked to safety and efficacy. In other words, quality can be defined as the safety and efficacy of the *next dose* a patient or consumer takes. In current practice, we ensure that a drug product meets appropriate quality standards or specifications. However, the frequency or degree of meeting the quality standard in manufacturing is not often measured, reported, or made publicly available. The FDA's recent initiative of quality metrics (FDA, 2016) is intended to fill some of this gap so that we have better understanding and knowledge of the state of product quality. These quality metrics are self-reported measures that provide quantitative and objective insight into the state of quality for product and facility. They can improve inspections, identify factors leading to supply disruption, and provide reliable information on quality that is readily understood by consumers. As a result, quality information can be a factor for consideration in the marketplace.

## 3. Performance-based regulation

Regulation may intervene at any of three stages of any organization's activities: the planning, acting, or output stages (Coglianese and Lazer, 2003). Potential outputs include both private and social goods (i.e., saleable products or services) as well as positive and negative externalities that affect society. Regulation is often needed when competitive economics drive private organizations to produce unhealthy social goods. In our case, this manifests in unsafe, ineffective, or low quality pharmaceuticals.

Regulations exist because companies failed to adequately ensure quality which resulted in tragic consequences. Indeed, the death of more than 100 people in 1937 across the United States from Elixir Sulfanilamide, a drug used to treat streptococcal

### Stages of Organizational Production and Types of Regulation



**Fig. 2.** Stages of organizational production and types of regulation.

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