The future of pharmaceutical quality and the path to get there

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**A R T I C L E   I N F O**

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**A B S T R A C T**

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**.

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**1. Introduction**

The U.S. Food and Drug Administration (FDA) Pharmaceutical Quality for the 21st 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 21st 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.
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
infections, led to the passage of the 1938 Food, Drug, and Cosmetic (FD&C) Act (Ballentine, 1981). Prior to the FD&C Act, safety studies were not required for new drugs. In the early 1960’s, women around the globe gave birth to children with severe birth defects as result of the sedative drug thalidomide. This drug was never approved in the United States, but the response to the global outcry led to the 1962 Kefauver-Harris amendments to the FD&C Act, which required drug manufacturers to prove that drugs were not only safe, but also effective (Hamburg, 2012). Each of these historical events, in its own way, shows how regulation responded to the needs of the market to eliminate unhealthy social goods and not vice versa. More recently, the global heparin crisis led to a sudden spike in serious adverse events after a contaminant, oversulfated chondroitin sulfate, was introduced into the heparin manufacturing process which went undetected by quality control methods (Sajek et al., 2016). In light of this and other events surrounding pharmaceutical quality, the FDA established a systemic focus on quality in a new Office of Pharmaceutical Quality to integrate review, inspection, surveillance, and research across the drug product lifecycle (Yu and Woodcock, 2015).

The ultimate goal of all regulation is to change outcomes by targeting regulatory intervention at any of the three stages: planning, acting, outputs (Fig. 2). Management-based approaches intervene at the planning stages, compelling regulated organizations to improve their internal management in an attempt to increase the achievement of public goals without negative consequences. Means-based approaches intervene in the acting stage, specifying technologies to be used or steps to be followed. Performance-based approaches intervene at the output stage, specifying or proscribing social outputs.

Two major variables that determine the effective use of a regulatory approach are (Coglanese, 2016): (i) the capacity to measure the output and (ii) the degree of homogeneity of the regulated entities across both location and time (Fig. 3). For industries in which there is a low capacity to measure output and low homogeneity of the regulated entities, management-based regulation is the preferred approach. On the other hand, for regulated entities with a high capacity to measure output, performance-based regulation is preferred.

For the regulation of pharmaceutical quality, we have traditionally used the management-based approach, meaning that regulatory authority is heavily involved in the planning stage of product development and manufacturing. We recognize that industry and regulatory authorities have used risk-based approaches to product development and control strategy establishment during marketing review to ensure in vivo performance. According to ICH Q8 (FDA, 2009c), a control strategy can include, but is not limited to, the following:

- Control of input material attributes (e.g., drug substance, excipients, primary packaging materials) based on an understanding of their impact on processability or product quality
- Product specification(s)
- Controls for unit operations that have an impact on downstream processing or product quality (e.g., the impact of drying on degradation, particle size distribution of the granule on dissolution)
- In-process or real-time release testing in lieu of end-product testing (e.g., measurement and control of critical quality attributes during processing)
- A monitoring program (e.g., full product testing at regular intervals) for verifying multivariate prediction models

The management-based approach brings burdensome regulatory requirements imposed on manufacturers for executing minor and incremental changes to manufacturing processes and controls, inhibiting continuous improvement and strategies for the implementation of continuous “real time” assurance of quality.

For drug substance and product manufacturing of small molecules, the capacity to assess output is high. Therefore, we can consider a move from management-based to performance-based regulation, meaning that regulatory authorities establish product specifications and encourage industry to improve the probability of meeting the product specifications. This may give the pharmaceutical industry flexibility to make changes, adopt new technology, and improve quality. However, for complex biopharmaceuticals the capacity to assess output is lower than in small molecule manufacturing and there could be challenges with a performance-based regulatory approach. As such, the most effective form of pharmaceutical regulation is the combination of management- and performance-based regulation in the near term, with the eventual goal of performance-based regulation only.

In many ways, the drive toward both six sigma quality and performance-based regulation of pharmaceutical manufacturing is predicated upon specifications that are soundly established based on clinical relevance. We recognized that manufacturers set specification limits based on several risk-based factors including: (i) the extent to which a critical quality attribute will have an impact on safety and efficacy of the product, (ii) an understanding of first principles associated with the drug substance and formulation, (iii) pharmacodynamics and pharmacokinetics of the drug, (iv) in vitro data corroborated by clinical results, and (v) variability of analytics, process manufacturing, and patient responses. Of course the connection between specification limits and product performance is more direct for some attributes (e.g., assay, impurities, dissolution) than others. These readily measurable attributes with a link to clinical performance form the foundation of performance-based regulation.

4. Pharmaceutical Quality by Design (QbD)

Pharmaceutical QbD is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management (FDA, 2009a). The key elements of QbD include: (i) a quality target product profile (QTPP) that identifies the critical quality attributes (CQAs) of the drug
product; (ii) product design and understanding including identification of critical material attributes (CMAs); (iii) process design and understanding including identification of critical process parameters (CPPs) and linking CMAs and CPPs to CQAs; and (iv) a control strategy that includes specifications for the drug substance (s), excipient(s) and drug product as well as controls for each step of the manufacturing process (Yu, 2008).

QTPP is a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product. QTPP typically includes administration, dosage form, route of administration, dosage strength, container closure system, pharmacokinetic characteristics, stability expectation, and drug product CQAs. The drug product CQAs are physical, chemical, biological, or microbiological properties or characteristics of a finished drug product that should be within an appropriate limit, range, or distribution to ensure the desired product quality. Attributes can be critical or not critical based on severity of harm to the patient should the product fall outside the acceptable range for that attribute.

The overall goal of product design is to develop a robust product that can deliver the desired QTPP over the product shelf life. Product understanding is defined as the ability to link input CMAs and CPPs to output CQAs. Strictly speaking, process and product design and development cannot be split since a formulation cannot become a product without a process. Process design is the initial stage of process development where an outline of the commercial manufacturing processes is identified on paper, including the intended scales of manufacturing. This should include all the factors that need to be considered for the design of the process, including facility, equipment, material transfer, and manufacturing variables. Steps to establish process understanding are very similar to those of product understanding (Yu et al., 2014). While developing a strategy for investigating both product and process design and understanding, studies can be designed in such a way that both the objectives of product and process understanding are achieved simultaneously. In addition, an interactive (or interdependent) relationship among material attributes, process parameters, and product attributes can be more easily developed in carefully planned and designed experimental studies.

The knowledge gained through product and process understanding forms the basis for establishing a control strategy. There are three levels of control strategy (Yu et al., 2014). Level 3 is the level of control traditionally used in the pharmaceutical industry. This control strategy relies on extensive end product testing and tightly constrained material attributes and process parameters. Level 2 consists of pharmaceutical control with reduced end product testing and flexible material attributes and process parameters within the established design space. Level 1 employs automatic engineering control to monitor the CQAs of the output materials in real time. Input material attributes are monitored and process parameters are automatically adjusted to assure that CQAs of an output material conform to the established acceptance criteria. When the control strategy moves from Level 3 to Level 1, greater assurance of product quality is achieved. Following QbD principles, process understanding coupled with a high level of process control can provide sufficient evidence that batches will meet specifications, allowing for potential real time release of batches. The direct outcome of using QbD for product development is the potential to increase process capability from 2 to 3 sigma to the goal of six sigma (Migliaccio, 2011) (Fig. 4). A genuine QbD may play the most important role in assuring consistently high product quality and robust manufacturing, as quality differences can often be directly attributed to the difference in product and process design and development.

5. Pharmaceutical emerging technology

FDA analysis of data collected from manufacturers indicates that production disruptions cause 66% of drug shortages (FDA, 2013). These production disruptions are often due to the use of outdated manufacturing technologies and equipment for drug substance and drug product production. Though the type of equipment/technology and the reasons for being outdated may vary, new technology is generally important for improving consistency and efficiency in manufacturing. Accelerating the development and adoption of pharmaceutical manufacturing innovations, so-called "emerging technology," is needed to realize the vision of six sigma quality. The FDA defined emerging technology as technology: (i) with the potential to modernize the body of knowledge associated with pharmaceutical development to support robust, predictable, and/or cost-effective processes or novel products and (ii) with which the FDA has limited review or inspection experience. Some relevant examples of emerging technology include continuous manufacturing of drug substance and drug product, "on-demand" manufacturing of drug products, use of robots in pharmaceutical manufacturing, 3D printed tablets, and new container and closure systems for injectable products.

Emerging technology can lead to robust manufacturing processes with fewer interruptions, fewer product failures, and greater assurance of product quality. Pharmaceutical manufacturing is still largely batch in nature and relatively inefficient, poorly understood, and poorly controlled as compared to other industries. A batch process is defined as one in which materials are charged into the system at the beginning of the process and the product is
discharged at once sometime later. In a true batch process, no material crosses the system boundaries between the time the raw materials are charged and the time the product is discharged. On the other hand, a continuous process is one in which materials are continuously charged into the system while the product is continuously discharged (Lee et al., 2015). Adopted by other industries, continuous manufacturing is one innovation that can lead to more efficient, better understood, and better controlled processes (Yu, 2016).

The process analytical technology (PAT) initiative from the turn of the 21st century provides the foundation of continuous manufacturing while the QBD effort of the past decade further fostered the development and adoption of continuous manufacturing for pharmaceuticals. A typical batch process employs a passive control strategy. After manufacturing, the output material is tested to determine if it meets the expected quality. If not, the material is reprocessed or discarded. In continuous manufacturing, an active control strategy controls the quality of output materials by adjusting process parameters (Fig. 5). In the theoretical ideal situation, the quality of output material is assured during manufacture.

The FDA has recently approved: (i) Orkambi™ (lumacaftor/ivacaftor), the first new drug application approved using a continuous manufacturing technology, and (ii) Prezista™ (daranavir), the first new drug application supplement approved for switching from an existing batch process to a continuous one. Continuous manufacturing offers numerous potential benefits, including reduced variability and increased reliability through the development and adoption of precise analytical technology and less reliance on labor-intensive manual activities. Costs can be reduced due to reduction in equipment footprints and labor needs, and increased process efficiency. Less processing time is required per unit dose (minutes vs. days). Scale-up bottlenecks can be eliminated leading to more agile and responsive supply chains. Importantly, increased capability enables rapid response to drug shortages, emergencies, and patient demand to ensure a consistent supply of high quality drug products (Yu et al., 2016). For many pharmaceuticals, continuous manufacturing is a necessity for realizing the six sigma vision.

6. Continuous improvement and operational excellence

Over the past 15 years, the FDA had a number of initiatives intended to improve product quality, including PAT, QBD, and Emerging Technology initiatives. These initiatives have largely been successful as the quality of newly introduced products is generally much higher (as illustrated in Fig. 4). However, the FDA has still been confronted with unprecedented drug shortages and product recalls, largely for legacy products, limiting patient access to critical drug products and undermining healthcare (FDA, 2015b; ISPE, 2017). Therefore, continuous improvement is a part of our overall effort to improve product quality, particularly for legacy products. Regulatory authorities need to create an environment and provide incentives for manufacturers to continually improve their manufacturing processes.

Continuous improvement is defined as recurring activity to increase the ability to fulfill requirements, which can be measured by process capability (FDA, 2009b). The process capability (Cp and Cpk) indices are obtained when calculations are based on the inherent variability, due to common causes, of a stable process (i.e., in a state of statistical control). A state of statistical control is demonstrated when the process exhibits no detectable patterns or trends, such that the variation seen in the data is believed to be random and inherent to the process (Yu et al., 2015; Peng et al., 2015). If the process is not in a state of statistical control, the calculations are based on standard deviation of all individual samples taken over a longer period of time. The result is the process performance index (Pp and Ppk).

A continuous improvement effort seeks to remove sources of inherent variability from the process operation conditions and raw material quality, resulting in higher process capability. Continuous improvement typically has five phases: (i) defining the problem and the project goals, (ii) measuring key aspects of the current process and collecting relevant data, (iii) analyzing the data to investigate and verify cause-and-effect relationships, (iv) improving or optimizing the current process based on data analysis (e.g., design of experiments), and (v) controlling the new process to ensure that any deviations are corrected.

Process variability can be common cause/inherent or special cause/intermittent. While continuous improvement reduces common causes, operational excellence directly controls special cause variability. On this front, special cause variability can be disastrous, resulting in significant financial loss and drug shortage. ICH Q10 describes a comprehensive model for an effective pharmaceutical quality system to direct and control a manufacturer’s ability to manage quality (FDA, 2009b). An operative quality management system (QMS) includes four elements: (i) a process performance and product quality monitoring system, (ii) a corrective action and preventive action (CAPA) system, (iii) a change management system, and (iv) management review of process performance and product quality. Knowledge and quality risk management enable a manufacturer to implement these four QMS elements.

Implementing these four QMS elements provides the foundation of product quality. The other critical enhancer is the culture of quality, an environment in which employees not only follow quality guidelines but also consistently see others taking quality-focused actions and hear others talking about quality (Sriniwasan and Kurey, 2014). A true culture of quality exhibits a range of easily recognizable attributes, including clearly visible, engaged, and unwavering senior management support for quality and clearly articulated vision, values, and quality goals. Active and ongoing engagement with customers continually identifies and addresses current and evolving needs. Performance expectations for all individuals throughout the company clearly link to quality goals and incentives (ForbesInsights, 2014).

According to some reports, world-class organizations are much more likely than others to exhibit the above attributes (ForbesInsights, 2014). They are also more likely to regard their quality capabilities as a means of creating and sustaining competitive advantage, leading to stronger profitability. As a result of their greater investment in and commitment to quality, these
organizations are in a better position to embrace continuous improvement and innovation, pursue and benefit from enabling technologies, and optimize risk-taking throughout the enterprise. It is important to note that even in the pharmaceutical realm, where the consumer is less able to recognize and reward quality, real benefits have been seen by companies embracing quality. One company’s pursuit of quality reduced the error rate 96% from 2006 to 2014 and generated cumulative saving of $400 million (Yu et al., 2016). With respect to avoiding shortages and recalls, patients also directly benefit from this pursuit of excellence.

7. Conclusion

The future of pharmaceutical manufacturing should be six sigma quality for both patient/consumer healthcare and economic reasons. On the patient side, eliminating drug shortages and recalls provides more reliability and less risk to the consumer. Equally or more importantly, six sigma can also help assure consistent performance, which is especially beneficial for minimizing efficacy or safety risks for complex and/or high risk products (e.g., Narrow Therapeutic Index drugs). On the manufacturing side, significant real-life cost savings can be the result of the drive to six sigma performance. To fully realize the benefits of six sigma quality, the pharmaceutical sector must introduce the economic factor society needs to recognize and pay for quality. At present, public self- or independent-reporting of quality measures and marketing focused on quality is not common in the pharmaceutical industry, though it is a major focus of other industries (e.g., automobile, consumer electronics). On the regulatory side of the equation, regulators need to move from predominantly management-based to performance-based regulation to give the industry enough flexibility to manage and improve quality on its own. In many ways, continuous manufacturing and advanced PAT are necessary to broadly advance toward six sigma manufacturing quality. To this end, the pharmaceutical sector must fully adopt QbD and vigorously advance and adopt new and emerging technology. Finally, continuous improvement and operational excellence must be part of the overall effort as patients and consumers depend not only on new drug products developed with QbD and advanced technologies, but also on legacy drug products. Although these collective principles outlining the path to the future may seem somewhat provocative, 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.

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References

FDA, 2013. Strategic Plan for Preventing and Mitigating Drug Shortages. 