21c Quality Management

in the Pharmaceutical Industry

The Journey from Compliance to Excellence

Edited by
Thomas Friedli
Prabir K. Basu
Christian Mänder
Nuala Calnan

EDITIO CANTOR VERLAG

21c Quality Management in the Pharmaceutical Industry

The Journey from Compliance to Excellence

Edited by
Thomas Friedli, Prabir K. Basu,
Christian Mänder, and Nuala Calnan

With contributions from
P. K. Basu, S. Biehl, M. Braun, P. Buess, N. Calnan, T. Friedli, S. Köhler, S. S. Lamba, B. Lehmann, N. Lembke, J. M. Lima, M. Lupo, C. Mänder, C. Moloney, N. Ponce, M. M. Reddy, and U. Schneider

ECV Editio Cantor Verlag Aulendorf (Germany)

Contents

1 Introduction

Thomas Friedli, Prabir K. Basu, and Nuala Calnan

Mere allocation of huge sums of money for quality will not bring quality.
W. Edwards Deming

1.1 From Operational Excellence to Quality Management

After publishing three books on Operational Excellence in the Pharmaceutical Industry (Friedli et al., 2006; Friedli et al., 2010; Friedli et al., 2013) in recent years, we have shifted our attention more and more to the underlying logic of successful and sustainable implementation of Operational Excellence (OPEX). While our first book was simply a status report on the industry (Operational Excellence in the Pharmaceutical Industry), we described OPEX in our 2010 publication as a never-ending journey (Pathway to Operational Excellence in the Pharmaceutical Industry). The following 2013 publication focused on cultural and leadership aspects of state-of-the-art Operational Excellence approaches (Leading Pharmaceutical Operational Excellence). Since then, partly because of severe quality issues and drug shortages, quality has regained center-stage in the pharmaceutical industry due to renewed consideration by the regulators.

In one of our presentations (Basu, 2014), we linked the ICH Q10 model to the St. Gallen OPEX model, focusing on the similar aims and the theoretical overlap of a respective metrics system. While preparing a presentation in 2015, Thomas Friedli (Friedli, 2015), changed the title of his presentation from *OPEX as basis for Quality* to *Quality as basis for OPEX* giving a clear indication how, based on his experience and available data from the St. Gallen OPEX Database, the two topics were intimately interlinked. This connection had always been apparent in the underlying logic of the St. Gallen OPEX model (as in other excellence models). Quality cannot be separated from OPEX. Quality operations lead to quality products. High quality processes result in high quality products, but over time also in higher efficiency. Quality and efficiency are the two sides of the same coin named excellence.

However, as the industry to a high degree still separates quality from OPEX, both organizationally and culturally, the conclusions of this connection have not been drawn adequately in most cases. The same is true in many other industries, as several high-level recalls and quality issues show. We believe that what is needed is a wake-up call, not only for the industry, but also for academia. Colledani et al. (2014) talking about production quality state that: *"traditionally, all these fields have been treated by scientists and industrialists almost in isolation. Yet it is clear that equipment availability, product quality and system productivity are strongly interrelated. As a matter of fact, quality, maintenance and production planning strongly interact and jointly determine those aspects of a company's success that are related to production quality, i.e., the company's ability to timely deliver the desired quantities of products that are conforming to the customer expectations, while keeping resource utilization to a minimum level."*

While the excellence models that were developed in late last century have theoretically solved the underlying problem of separating quality from general management, pushing the attention to the need for integration and stopping the practice of managing quality as a specialized function, this message has obviously not been translated into the day-to-day realities of today's industrial enterprises. In this book, we will make another attempt to contribute to an integrated management of quality. This is in line with the thinking of one of the most prominent quality management gurus, Edwards Deming, who proposed the *theory of profound knowledge* which states that the success of quality management efforts depends on the effective integration of various management subsystems (Deming, 1998). This time we will attempt to integrate quality and OPEX using the data compiled from our extensive research in Operational Excellence over the last twelve years. This does not mean that we will deviate from Operational Excellence, as we still believe that Operational Excellence is the overarching framework embracing and being built on quality. Now, our effort will focus on the attempt to align the quality function with operational excellence. This could become a real competitive advantage for the companies being the first to implement such an integrated approach.

These companies will additionally be the ones to see an opportunity and not a threat in the new regulatory interest in quality management and quality metrics. Therefore, we focused our research over the last two years to develop a complementary model to the well-known and established St. Gallen OPEX model which is the St. Gallen Quality Benchmarking Model. This will hopefully help industry overcome the existing divide between Quality and Excellence. This model is in line with the comment made by Victor Prybutok from the University of North Texas who commented that *"... the future of quality management is dependent on the development of unique and specific quality management models ..."* (Evans, 2013). It additionally highlights the underlying relationships between quality and operational performance, therefore contributing to quality theory addressing an existing gap that had also been identified by Fredendall (Evans, 2013).

The first results of applying this model, together with the interest driven by the FDA's quality metrics initiative, convinced us to write a book about 21st century Quality Management for the Pharmaceutical Industry. Considering the quality issues we have experienced over the last decade from automotive to electronics and from aviation to pharma, we believe that some of the thinking presented in this book could make a difference in other industries too. The winners in tomorrow's business landscape will be the companies who are able to manage from an overall system perspective, not sacrificing long-term success for short term profits.

1.2 Quality in the Spotlight

1.2.1 Quality Issues across Industries

Several high-level recalls and quality issues have brought back quality center-stage in recent years. General Motors, Toyota, Porsche and Baxter to name only a few have made visible that despite decades of improvement in the management of quality, it still seems not or no longer to be mastered. Especially worrisome is that the very foundation of every state-of-the-art Total Quality Management (TQM) system, which is the commitment of leaders and employees to think and act in quality, has been revealed as the weak link in the chain in more than one case. Despite seminal advancements in the field of quality management, more quality-related problems than ever are making the headlines (Flynn & Zhao, 2014). Schneider (2016) comments that the overall number of quality management implementation failures is significant. Studies show that the share of imple-

mentation failures are as high as 80% (Cândido & Santos, 2011; Tata, Prasad & Thorn, 1999; Taylor & Wright, 2003).

Cândido and Santos (2011) designate several reasons for the diverging study results. For instance, the different underlying definitions of quality management failures. Besides, the authors suggest that the results indicate a decreasing trend in implementation failures. However, this decrease could be based on the adaption of the Quality Management (QM) strategies to the prevailing context, but failures will increase again when this contextual environment changes. As we experience unprecedented globalization in the area of customers and markets, as well as on the global supply chain level, we believe that standard quality management system (QMS) implementation no longer fulfils the requirements. Since every single plant in a global supply chain has different capabilities and a different culture, how can we expect that standard implementation of total quality management will be able to deal with the separate and individual realities?

What is needed is the possibility to design a quality system on the plant level, specifically adapted to the individual plant realities. The pre-condition to do this systematically is a quality management model that helps to analyse the relevant levers (enablers) and the respective outcomes to derive the right conclusions for optimization. One of the main outcomes of this book will be the development and data-based validation of such a model.

1.2.2 Quality Discussions in the Pharmaceutical Industry

In the world of pharmaceutical production, it is universally understood that a robust pharmaceutical quality system provides key elements of assurance and oversight for pharmaceutical manufacturing processes. It ensures that patients are provided with medications that are safe, effective, and reliably produced at a high level of quality. However, despite recent advances in the manufacturing sector, quality issues remain a frequent occurrence, and can result in recalls, withdrawals, or harm to patients. Quality issues have also been linked to the rise in critical drug shortages (ISPE, 2013).

Regulatory agencies currently assess the risk profile of manufacturing sites based primarily on their compliance history, as seen in warning letters and field reports, in conjunction with records on product recalls and market-based quality problems. These are not necessarily the most informative measures, and by their nature, provide historical or lagging data. More relevant data relating to the state-of-quality, provided in advance, would better inform the risk factors that might predict quality problems and future drug shortages.

The FDA's approach to quality oversight has evolved in recent years, and the new Office of Pharmaceutical Quality (OPQ) has made it a priority to establish a sounder basis for ensuring that pharmaceutical products meet high quality standards throughout the product lifecycle. Since early 2013, the FDA has been working with the pharmaceutical industry to develop goals and objectives for a quality metrics program. In response, several industry stakeholder groups have worked with the FDA to develop consensus around the goals, as well as to identify potential metric sets, including developing recommendations for their implementation and interpretation. Through a series of extensive engagements between industry and the FDA, there has been an acknowledgement of the complexity of the problem at hand, namely to develop a recommended set of metrics which are objective and meaningful, easy to capture, yet normalized to account for factors such as process differences and technical complexity.

Furthermore, it is required that those elements selected will promote acceptable behaviors and not lead to any unintended consequences or unwanted behaviors. At the end of July 2015, the FDA released its draft guidance entitled *Request for Quality Metrics – Draft Guidance for Industry* which captures the relevant aspects for meaningful quality metrics. The guidance gives the background

and intended purpose of use for the quality metrics. Furthermore, it addresses the legal authority and the use of the metrics, including the effects of non-reporting. In the last section of the guidance, the FDA introduces the reporting of quality data and the logic behind the quality metrics calculation. The following metrics have been proposed in the industry guidance:

1. Lot Acceptance Rate
2. Product Quality Complaint Rate
3. Invalidated Out of Specification Rate
4. Annual Product Review or Product Quality Review on Time Rate

Furthermore, the FDA proposed three optional metrics related to quality culture and process capability. In addition, the FDA issued a request for comment related to the data reporting frequency that needs to be levelled according to a risk based scheme (FDA CDER, 2015). In November 2016 already, the FDA released a revised draft guidance focusing on three metrics only (Lot Acceptance Rate, Product Quality Complaint Rate and Invalidated Out of Specification Rate) (FDA CDER, 2016). We will return to this revised guidance in chapter 11, see page 194.

Quality metrics are widely used throughout the pharmaceutical industry to monitor quality control systems and processes, and many of the components that inform those metrics (e.g., data on process capability output or statistical process control) are already collected and maintained as part of cGMP compliance. Several measures of performance are already common throughout the industry. The challenge is that they are currently defined differently across manufacturers, and even between sites operated by the same manufacturer. The proposed FDA Quality Metrics program is not the first of its kind; rather, it draws from the example of existing private sector quality improvement programs that collect voluntarily reported, standardized quality metrics from a large and varying array of manufacturing sites, which are then used by participating manufacturers to benchmark their performance against industry standards and their peers.

The collection and analysis of standardized quality metrics can serve several functions:

- At a basic level, metrics should provide a quantitative and objective measure of quality at the manufacturing site, and provide a window at a systems level to the effectiveness of the oversight and control of operations at a given site.
- Metrics data collection and analysis should also help mitigate or reduce quality related drug shortages and recalls by allowing for early identification of products at risk of quality failures.
- Metrics provide an opportunity to stratify manufacturing sites according to quality risk and thus prioritize scarce regulatory resources for inspection of plants worldwide.
- Ultimately, these metrics should assist pharmaceutical manufacturers to promote positive behaviours and a corporate culture of responsibility for quality, by providing incentives to improve product and process capability.

Thus, quality metrics may contribute to ongoing broader FDA efforts to reduce risk and improve drug quality.

This book will help to define an approach as to how to deal with and fulfil the requirements of this new regulatory approach, but also to make use of this regulatory push to finally integrate quality and operational excellence into an overall management system. Companies focusing only on the three reportable metrics will not achieve the required shift towards real excellence management. It will also not be sufficient to simply adapt total quality management approaches from other industries. We have shown above that they simply do not match the current challenges. The globalization effect that has made an impact on other industries, such as automotive, electronics, etc., will

also be felt in the same manner in pharma today and tomorrow. Therefore, it would be unwise to simply copy recipes from the past.

1.2.3 Some Conclusions

The challenge for manufacturers across industries to manage quality successfully is tremendous. Well established excellence models based on TQM concepts no longer seem able to deliver the required quality as intended. The pharmaceutical industry is additionally challenged by new regulations. We believe that the main problem does not lie in the basic designs of existing excellence models and quality management systems, but in the way they are organizationally embedded and managed. As there still seems to be a basic belief that there is an inherent trade-off between traditional quality objectives and business related outcomes, quality and excellence are not truly integrated, but in a lot of cases managed as opposite aims. This situation is worsened by consultants translating excellence as cost and pushing industry to cost cutting exercises, eroding the basis for stability and therefore endangering the capability to sustainably deliver the required quality.

1.3 Objectives of this Book

Our book is aimed at providing the industry with a new approach to manage quality. This approach will be based on a true system understanding of manufacturing sites and will help to overcome the divide between quality and operational excellence. To make this approach sound, we will develop a new quality management model and evaluate it based on extensive data analysis. We hope that this data-informed discussion will be more powerful and will result in a faster and deeper impact on the industry rather than having a merely qualitative discussion. At the same time, this approach could also become a role model for other industries, as it will also be a *first* across industries, revealing the data-based interdependencies between quality and excellence. Additionally, this book will inspire companies to seriously embrace the FDA's approach to quality metrics and use it as a chance to increase their competitiveness.

1.4 Structure of the Book

This book is structured in four parts and 18 chapters. In the first introductory part, we lay the foundations for a new approach to manage quality. In the first chapters we describe the paradigm change resulting from moving the industry from compliance-based thinking to excellence based thinking in accordance with the St. Gallen Quality Management Model.

The second part of the book is focused on deepening the understanding of some selected enablers to manage quality in a new way.

The third part highlights different case studies from the field, describing the challenges, as well as the opportunities that come with an integrated management of quality and excellence.

The fourth part summarizes the main findings and provides an outlook to an even broader system-based approach to quality management, based on a research project at the University of St. Gallen funded by the US FDA (Friedli et al., 2017).

References

Basu (2014). OPEX and Quality: Operational Excellence – can it be the metrics for a robust quality management system? Presentation at Research Group Meeting, Chicago, USA, from 30. 04. 2014.

Cândido & Santos, 2011. Is TQM more difficult to implement than other transformational strategies? Total Quality Management, 22(11), 1139–1164.

Colledani, M., Tolio, T., Fischer, A., Iung, B., Lanza, G., Schmitt, R., & Váncza, J. (2014). Design and management of manufacturing systems for production quality. CIRP Annals – Manufacturing Technology, 63, 773-796.

Deming, W. E. (1998). Out of the crisis (26. print). Cambridge, Mass.: Massachusetts Institute of Technology.

Deming, W. E. 2000. Out of the Crisis. Cambridge, Mass: The MIT Press, 2000.

Food and Drug Administration (FDA). (2015). Request for Quality Metrics: Guidance for Industry. Retrieved 20 September 2017 from https://www.seikiken.or.jp/document/dg_20150727.pdf

Food and Drug Administration (FDA). (2016). Submission of Quality Metrics Data: Guidance for Industry. Retrieved 20 September 2017 from https://www.fda.gov/downloads/drugs/guidances/ucm455957.pdf

Flynn, B. B., & Zhao, X. (Eds.). (2014a). Global supply chain quality management: Product recalls and their impact. Boca Raton, FL, USA: CRC Press.

Evans, J. R. (2013). Insights on the Future of Quality Management Research. Quality Management Journal, 20 (1), 48-55.

Friedli, T., Koehler, S., Buess, P., Basu, P., & Calnan, N. (2017). FDA Quality Metrics Research: Final Report – Year 1. Retrieved from http://tectem.ch/institute/opex/fda

Friedli (2015). Quality as Foundation for OPEX. Presentation at PDA Europe Conference „Universe of pre-filled Syringes", Vienna, Austria, from 4. 11. 2015.

Friedli, T., Werani, J., Basu, P. K., & Gronauer, T. (2010). The Pathway to Operational Excellence in the Pharmaceutical Industry: Overcoming the internal inertia. Aulendorf: Editio Cantor.

Friedli, T., Basu, P., Belm, D., Werani, J. (2013). Leading Pharmaceutical Operational Excellence – Outstanding Practices and Cases. Berlin: Springer.

Friedli, T., Kickuth, M., Stieneker, F., Thaler, P., Werani, J. (2006). Operational Excellence in the Pharmaceutical Industry. Aulendorf: Editio Cantor.

Food and Drug Administration (FDA). (2013). Strategic Plan for Preventing and Mitigating Drug Shortages. Food and Drug Administration. Retrieved 20 September 2017 from https://www.fda.gov/downloads/drugs/drugsafety/drugshortages/ucm372566.pdf

Schneider, U. (2016). An Implementation Process Framework for Quality Management in Global Manufacturing Networks: A Contingency Perspective Towards Global Quality Management (Dissertation). University of St. Gallen, Switzerland.

Tata, J., Prasad, S., Thorn, R. (1999). The Influence Of Organizational Structure On The Effectiveness Of TQM Programs. In Journal of Managerial Issues Vol. 11, No. 4 (Winter 1999), pp. 440–453.

Taylor, W. Andrew; Wright, Gillian H. (2003): A longitudinal study of TQM implementation. Factors influencing success and failure. In Omega 31 (2), pp. 97–111.

All links accessed 14. 02. 2018.

2 Understanding the Impact of the Changing Regulatory Environment on the cGMPs and the Industry

Prabir K. Basu, Nuala Calnan, and Thomas Friedli

2.1 Introduction

2.1.1 Drug Quality in the 21st Century and Pharma Manufacturing

Quality has been defined by many researchers and quality professionals. For example, Juran (1979) defined quality as *fitness for use*. Crosby (1979) defined quality as *conformance to specification*. Quality is also defined as *customer satisfaction*, *degree of excellence*, *ability of a product to perform its intended function in satisfactory manner or failure free*, etc. The quality of a product is an integral part of its specification for manufacture. The concept of quality existed long before the concept of productivity. However, there existed a belief till the first half of the twentieth century that productivity and quality are in a trade-off relation to each other. During the twentieth century, the Japanese automobile industry, with help of people like W. Edwards Deming, proved that making good quality product also improved productivity while reducing cost and avoiding waste. Other quality gurus such as Philip Crosby, and J. M. Juran have long advocated the positive relationship between productivity and quality performance. In fact, Deming's assertion is that as quality improves, costs decrease because of less rework, fewer mistakes, and fewer delays (Deming, 1993). There is no doubt that quality directly or indirectly affects productivity and cost of the product. In fact, it is now accepted by all in developed countries and as well as in developing countries that improving quality and implementing quality management tools help companies maintain their position in the market and to even improve market share. It is obvious that quality and productivity are positively related to each other.

By drug quality, we commonly mean quality of the drugs that are available on the pharmacist's shelves. There is no doubt that the quality of drugs, by this definition, is very high and pharmaceutical companies spend significant resources to ensure this remains so. However, in the early 21st century (Woodcock, 2004), the pharmaceutical industry, the U.S. Food and Drug Administration (FDA) and the regulatory agencies in Europe and Japan realized that though the quality of marketed pharmaceutical products was high, there was much to be improved in the quality of the manufacturing processes and the quality of the drugs as they were being manufactured. If this could be achieved, it would not only significantly increase the probability of assuring quality of drugs that are sold to patients by the pharmacists, but it would also make the job of the regulating agencies much easier, especially in this ever-expanding global drug supply chain environment.

The quality of marketed pharmaceuticals is achieved by inspection and not by design which is exactly what quality exponents like Deming were professing against. In fact, Deming's 3rd point in his 14 points in Total Quality Management is as follows (Deming, 1993):

"*Cease dependence on inspection to achieve quality. Eliminate the need for massive inspection by building quality into the product in the first place.*"

The idea that quality should be built into the design of the products and into the processes to manufacture them, has come to be generally accepted in the past 50 years, and implemented in many industries. In those industries, there are never any arguments against it. At the same time, final inspection and test has never completely disappeared. Inspection is a manual process, subject to human error and that is why Deming describes it as ineffective as a filter for defectives.

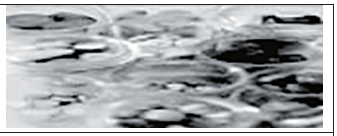
Because pharmaceutical manufacturing processes have high variability, manufacturing and the quality of products manufactured are variable (Morris, 2006). While pharma companies have traditionally excelled in new product discovery, they have not necessarily been at a world class level in manufacturing quality and manufacturing efficiency. Since the last two or three decades, pharmaceutical companies have been under the competing pressures of innovating, increasing growth, and accelerating time-to-market while maintaining product quality (McCormick, 2003). Benson (Benson & McCabe, 2004) discussed various measures to benchmark manufacturing performance and compares the pharmaceutical industry with a world class manufacturing company in respect to the measures discussed. Benson's analysis shows the tremendous opportunity that pharmaceutical manufacturing plants have to improve performance. Though it is not quite evident on the surface, however, the quality of the products manufactured is directly related to the manufacturing science and technology employed and manufacturing efficiency and effectiveness. Though cross-industry comparisons on a single KPI to single KPI level have only limited meaningfulness, as the underlying process to be compared are quite different, room for improvement can be shown in intra-industry comparisons.

Out of Specification (OOS) investigations, deviation investigations and other unplanned interruptions not only take significant time and resources, but result in a manufacturing operation which has low efficiency and high cost. Dean (Dean & Bruttin, 2005) referred to unmet performance expectations of pharmaceutical manufacturing due to inherent low process capability. As a result, the utilization levels were low ($< 15\%$), scrap and rework was high, and cost of quality was in excess of 20%. Hussain (2004) defined the state of pharmaceutical manufacturing in early 2000 as static and based predominantly on empirical approaches. Hussain emphasized that fundamental science and engineering principles are less well-developed than in other industries.

It is well known that pharma processes tend to produce many more defects even than other regulated industries such as the aerospace or the nuclear industry (table 2-1). The reliability of aircraft and nuclear plants is much higher (much greater than six sigma) than pharmaceutical processes which are known to be poorly designed. *"The pharmaceutical industry produces six-sigma products with three-sigma processes"* (The Goldsheet, 2002). In fact, that is why there was such a push by industry and the FDA to implement initiatives like the 21st century cGMPs, Process Analytical Technology (PAT), the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), and Quality by Design. It is very important for pharma processes to be designed well and then monitored carefully to detect systemic failures such that these failures can be rectified early enough during manufacturing before the product is inspected and released for the market. An often quoted saying during the early 2000s, was *"... the only way Pharma prevents defective products from reaching the market is to have a six-sigma quality process"* (The

Goldsheet, 2002). That is why it is so important for the quality systems and quality processes to work in Pharma. It protects sick patients from defective and ineffective products.

Table 2-1. Pharma manufacturing does not fare well compared with other regulated industries.

			
Regulated Industry	yes	yes	yes
How is Quality Ensured	Quality by Design	Quality by Design	Quality by Inspection
How is Product and Process Designed	detailed model-based design	detailed model-based design	empirical, minimal use of models, multiple scale-ups
Defect Rate	extremely low, >>> Six Sigma	extremely low, >>> Six Sigma	high, Two to Three Sigma
Raw Material Specification	very rigid and controlled	very rigid and controlled	raw materials have variable properties
Status of Technology	well developed technology	well developed technology	technology for product dev and mfg not well developed

We often hear that the reason why pharma manufacturing is lagging behind other industries in sophistication and quality of products manufactured, is because pharma is regulated while other industries are not. Here is a quote by a pharmaceutical manufacturing professional from a Pharmaceutical Forum published in the European Industrial Pharmacy (2010, p. 5), "*... I spent sixteen years in the aviation industry, during which time QA and QC took over the whole industry and when incidents through faulty manufacture virtually disappeared. We started to see year on year no incidents attributable to technological faults. As systems were automated the human input was reduced. Clever design made it more and more difficult for the remaining human input to jeopardize safety. However, until all the remaining human input is replaced by technology, muddled thought processes can and will often fail to interact correctly with highly technical systems. Now after sixteen years in the pharmaceutical industry let me say that this industry is nowhere near the standard of compliance that is considered adequate in aviation. Were any auditor from the aviation industry to apply aviation standards during pharmaceutical audits, they would close most, if not all, pharmaceutical plants.*"

Regulations are not and should not be blamed for relatively poorer quality of manufactured products in pharma compared to industries such as the auto industry, the electronics industry or the aerospace industry. In fact, the true reason for poor quality in pharma is that the tools used to measure and control variability in manufacturing, which have been used by other industries since the middle of the twentieth century, are only being seriously considered by pharma now, after the FDA industry initiative to modernize pharma manufacturing began in the early 21st century. Even then, these tools are currently only being used selectively by a few companies for a few of their products (Ceglarek, 2013).

Derek Ceglarek, University of Warwick, (Ceglarek, 2013) explains the evolution of manufacturing from 1913 with mass production of automobiles by Henry Ford, with the evolution of lean, then flexible manufacturing systems in the 1980s, and now with reconfigurable manufacturing systems

in the 21st century (Koren & Shpitalni, 2011). In the 21st century, companies must design manufacturing systems that not only produce high-quality products at low cost, but also allow for rapid response that can meet changing business goals. Reconfigurable manufacture is novel and facilitates cost effective and rapid responses to market and product changes.

2.1.2 Vision for Pharma Manufacturing

Dr. Janet Woodcock, FDA eloquently defined FDA's vision of 21st century quality as (Iser, 2014) *"A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight."* This vision is in line with what manufacturing is in other industries in the 21st century as illustrated above. Pharmaceutical manufacturing today is not flexible and definitely not agile and efficient. It requires high internal quality oversight and external regulatory oversight. The main reasons behind this is the high variability and unpredictability of manufacturing processes, the lack of ability to take corrective actions before the variation is likely to occur, the lack of continuous improvement and inflexibility of certain regulations such as change-control.

2.1.3 Operational Excellence – a Pathway to Pharma Manufacturing Vision

To meet Dr. Woodcock's vision, there is no doubt that pharma manufacturing needs to embrace operational excellence. Operational excellence (OPEX) is a state in which an organization constantly executes consistently and reliably. Operational excellence is achieved through leadership, teamwork, reducing variability in operations and problem solving resulting in continuous improvement throughout the organization while focusing on the needs of the customer, empowering employees, and optimizing existing activities in the process.

Operational excellence in manufacturing is directly related to agility, flexibility and efficiency of manufacturing operations. Quality is the outcome of manufacturing and operational excellence, and this quality does not come at any added cost, but it is associated with significant cost savings. It is well recognized that the elements which are essential in an efficient and agile operation are also responsible for improving quality of products, manufactured by that operation. Operationally excellent organizations develop specific competences – related to cost management, quality management and process excellence – that allow them to offer the better service to their customers. A common element shared by all involved with pharma manufacturing is that to improve pharma manufacturing to the 21st century standards and to attain Dr. Woodcock's vision, variability in manufacturing should be reduced. According to Orloff (2014), reducing variation to improve quality would lead to minimized costs and maximized profits while reducing risk to the patient. Orloff also contends that the *"key to a 'maximally efficient, agile, and flexible industry' could be a single meaningful metric to focus attention on process variation and separate regulatory oversight into distinct departments for compliance and performance. This metric is the out-of-specification (OOS) rate."* When products and processes are designed with little process understanding, performance is left to chance and is the root cause of high variability in manufacturing. The ability to predict product performance also reflects a high degree of process understanding. That is exactly the goal of all OPEX programs. Manufacturing plants that have implemented 21st century OPEX programs do not complain about regulations. They know that quality is an obvious outcome of their OPEX programs. It would be highly logical if the FDA would consider giving more flexibility to making changes to equipment and processes where the plant has high quality OPEX programs in place. That would be an added incentive for such companies who are already motivated to excel.

2.2 FD&C Act – Drugs Defined; cGMPs, History of cGMPs

Current Good Manufacturing Practices or cGMPs were designed by regulatory authorities to describe what is necessary to manufacture safe and effective drugs. In fact, the FDA argues that only regulatory oversight offsets the corrupting effect of the corporate profit motive, which creates conflicts of interest between corporations and public health (Braithwaite, 2013; Gagnon, 2013). Essentially, cGMPs provide a set of best practice standards that pharmaceutical manufacturers are required to adopt and incorporate into their drug-making processes. However, often pharmaceutical manufacturers complain that either the regulation is too restrictive and descriptive or it does not define exactly what needs to be done to manufacture high quality pharmaceutical products while following the regulation. But, if one carefully reviews the cGMP regulations, including the associated guidance documents, it is evident that these have actually been designed to enable drug manufacturers to incorporate the best, most up-to-date manufacturing technologies and processes into their standard operations to assure drug quality and therefore drug safety. There is apparently a lack of understanding of the principles and applications of the cGMPs by some industry representatives. The appreciation for the cGMPs comes with training and education. This understanding of the regulations comes with years of experience and with the development of a compliance and regulatory culture in a firm.

The regulation, based on many years of experience, strongly supports public health and well-being. According to Kandle (1969, p. 9-13) "*In a broad sense, the regulations, commonly called GMPs, detail what one would simply refer to as 'good business'. If for no other reason, both the entrepreneur and the investor in the drug industry should favor such good drug manufacturing practices. Certainly, neither would, with prudence and good will, involve himself with an unsanitary, unsafe, inadequately equipped drug manufacturing facility. By efficient use of modern GMPs, it should be possible for industry to reduce costs and forestall a rise in the prices of drugs.*"

Approval of the selected manufacturing standards and procedures outlined in a new drug application (NDA) or an abbreviated new drug application (ANDA) or an associated Pre-Approval Inspection, does not shield a company from FDA action if the process generates failures to comply with cGMP regulations. The Federal Food, Drug and Cosmetic Act (FD&C Act) (1988) specifically mentions conformity with cGMP in relation to medical drugs and devices.

"*501(a)(2)(B) of the Act requires the methods, facilities, and controls used in the manufacture, processing, packing and holding of a drug product to conform to current good manufacturing practice in order to assure that the drug meets the safety requirements of the Act and that the drug has the identity, strength, quality, and purity which it purports to possess. Section 520(f)(1)(A) authorizes the Secretary of Health, Education and Welfare to prescribe regulations requiring conformity with CGMP in the manufacture, pre-production design validation, packing, storage, and installation of medical devices."* and *"Section 501(a)(2)(B) of the Act does not provide the Secretary with the authority to promulgate CGMP regulations relating to the manufacture of drugs. The Secretary derives the authority from Section 701 of the Act, which gives the Secretary the authority to prescribe regulations for the efficient enforcement of the Act. Federal Food, Drug, and Cosmetic Act _701(a), 21 U.S.C. _371(a) (1988 & Supp. V).*"

Under Section 501(a)(2)(B) of the Act, a drug is considered to be adulterated if the manufacturer did not comply with the cGMP regulations during production even if the product was technically perfect. Regulations for current good manufacturing practices guidelines within the 21 CFR are promulgated by the Commissioner of the Federal Food and Drug Administration under Section 701 (a) of the Federal Food Drug and Cosmetic Act [21 United States Code 351 (a)(2)(B)]. This regulation

specifies that a drug is considered to be adulterated "*if methods used in, or the facilities or the controls used for its manufacture, processing, packing or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice*" (Goldstein, 1995). By following the cGMPs, manufacturers should be able to establish reasonable practices and procedures to enable them to produce pharmaceutical products in a manner such that it will reduce the possibility of a manufacturing process to produce an adulterated product (Hagenbush, 1983). The intent of the law was twofold: to *insure the dosage-integrity of drugs* by preventing the development, production and distribution of faulty drugs which invariably result from faulty manufacturing practices, and to provide the enforcement authority to correct faulty operations *before* drugs of questionable integrity result there from. In substance, a drug will be deemed to be *adulterated* if the methods or the facilities or controls *"do not conform to or are not operated or administered in conformity with cGMP to assure safety, identity, strength, quality and purity."*

Thus, a drug would be deemed to be adulterated if the method or facilities or control (production and quality controls) do not conform to cGMP. What is indeed significant is that a drug which is not in fact adulterated will also be deemed to be so if it does not conform. "*In its intent, this requirement is certainly reasonable, as a sanctionable statutory standard which should define or establish a rule or required course of conduct, the statutory words 'Current Good Manufacturing Practice' are no more definitive than an admonition to 'be good or else.' The words are vague in that they do not: (a) permit a manufacturer to define what is the standard of good industry practice, or (b) provide a basis for evaluating the state of operational compliance. And since industry production and quality control practices are in a state of constant change, the statutory standard is, itself, fluid changing constantly*" (Jeffries, 1968).

"In the Barr Laboratories decision, the court suggests that when the CGMP regulations create ambiguities, industry can obtain further guidance from seminar and pharmaceutical firm literature, textbooks, reference books and FDA letters to manufacturers. Companies cannot use industry standards alone to settle questions of CGMP compliance, however. According to the Barr Laboratories court, industry standards themselves must be reasonable and consistent with the spirit and intent of the CGMP regulations. In addition to these other sources, companies can rely upon FDA guidelines addressing CGMP compliance" (United States v. Barr Laboratories Inc., 1993). As long as the practice is *good* and it is feasible for manufactures to implement, it should be considered as *minimum*. For example, it is a *good* practice to implement systems to enable a manufacturer to monitor and detect defective products, and to take rapid and appropriate corrective actions to rectify its operations to assure safety, quality or purity of the drug product being manufactured.

2.2.1 What is cGMP?

Good Manufacturing Practice or GMP is a set of principles and procedures which, when followed by manufacturers of therapeutic goods, helps ensure that the products manufactured will have the required quality. The procedures and practices stress that products being manufactured are consistently manufactured to the quality standards appropriate to their intended use. The c in *cGMP* stands for current to emphasize that the expectations are dynamic. It is expected that standards evolve with time. Good Practices imply *minimal standards* and not necessarily *best practices*, unless *best*, is in fact, current minimal. The ultimate purpose of cGMPs is to assure the safety and efficacy of the finished products. *"The regulations, based on decades of experience, are a strong support in the protection of public health. They spell out for companies, large and small alike, what procedures are required in terms of current good practices. They impose* ***no*** *undue burden upon legitimate business, but they deter substandard operators who cut corners and gamble with careless operations which pose serious hazards to public health. The federal regulations, first promulgated in*

1962, have aided enforcement agents to close down unfit operations, and to help bring substandard companies up to par" (Kandle, 1969).

As part of its responsibilities under the Federal Food, Drug, and Cosmetic Act, the FDA monitors the manufacturing practices of companies involved in the production of food, drugs, and medical devices. By including the requirement of compliance with cGMP in the statute and by promulgating cGMP regulations to guide manufacturers, the United States Congress and the FDA underscore the important connection between the quality of the process and the quality of the finished product.

"Vague and fluid as the statute may be in its words, the intent is reasonable, and to implement both the intent of Section 501 (a)i (2) (B), FDA promulgated the interpretive CGMP regulations providing industry with "general guidelines" setting forth minimum requirements or standards defining what 'current' GMPs consist of, and these standards were supplemented by additional requirements imposed through new drug certification procedures. ...

And since, as indicated earlier, the minimum requirements or standards defined as 'current' GMP are subject to change as experience and scientific and technological development indicate a need for redefinition, this means that as a manufacturer's products become more complex and his processing more complicated, so must his controls, in order to maintain his quality assurance objectives. In effect, it becomes the manufacturer's duty and responsibility to develop and establish the character and configuration of GMPs 'currently' needed to achieve dosage-integrity for his product. It could, for example, mean that with the introduction of a new, ultra-high-speed tablet compressing unit or high-speed packaging and labeling equipment, good manufacturing practices might require material modifications in applicable quality assurance control protocols and procedures to insure product integrity and establish an appropriate state of CGMP compliance" (Jeffries, 1968).

2.2.2 Why Follow cGMPs?

According to Steve Lynn (2013), *"It's the law – Food Drug and Cosmetic Act (FD&C):*

501(a)(2)(b): requires conformity w/ CGMP. It is Codified in 21 CFR 210 & 211. Thus, Not following CGMP regulations constitutes adulteration under the Act:

- A *drug*... shall be ***deemed*** **to be** ***adulterated*** if... the *methods* used in, or the *facilities* or *controls* used for, its *manufacture*, *processing*, *packing*, or *holding* do not conform to or are not operated or administered in conformity with ***current good manufacturing practice***...
- to assure that such drug meets the requirements of this Act as to ***safety*** and has the ***identity*** and ***strength***, and meets the ***quality*** and ***purity*** characteristics, which it ***purports*** or is ***represented*** to *possess."*

According to the FDA (FDA, Facts About the Current Good Manufacturing Practices (cGMPs)), *"CGMPs provide for systems that assure proper design, monitoring, and control of manufacturing processes and facilities. Adherence to the CGMP regulations assures the identity, strength, quality, and purity of drug products by requiring that manufacturers of medications adequately control manufacturing operations."* Therefore, to assure the *identity, strength, quality and purity of the drug products*, all processes and equipment manufacturing a medicinal product in a cGMP operation should be made stable and reduced to low levels of defects, i.e., made capable. It is the responsibility of the manufacturer therefore to ensure that the process used to manufacture a drug product for sale in the U.S. market is stable and capable.

Thus, the basic idea of cGMP is that the cGMP systems, if implemented properly, allow a manufacturer to be proactive and not react to problems. Reacting to problems is the clearest sign of an *out of control* operation. Deming (1950) states "*Good quality means predictable degree of uniformity*

and dependability." *Predictable degree of uniformity* could be inferred as *predictable degree of variability*. The *Pharmaceutical CGMPs for the 21st Century - A Risk-Based Approach* (August 2004) is specifically aimed for pharma manufacturers to use a risk-based approach in implementation of their cGMPs so that they can foresee problems rather than reacting to them. According to Mr. Anisfeld, a well-known cGMP consultant, "*Design your manufacturing and laboratory system well, and keep in mind that our products are taken on trust and that our potent products will be ingested by our grandparents and by our children–the most vulnerable in society*" (Anisfeld, 2013).

Ideally, all products and processes should be designed to be stable and capable at start-up. However, in practice, most processes and products, along the way, require some improvements and sometimes extensive improvements to make them stable and capable. New processes should therefore have safeguards in place until such time as the processes are proven stable and capable. Even if a process starts up trouble-free or the product does not have any measurable defects at start-up, it does not guarantee that no problems will occur in the future. Equipment breaks and wears, people change, raw materials change and conditions change. Thus, rigid monitoring and controls, and revalidation must be put in place to develop the quality history of the process.

The sampling, monitoring and controls used in a manufacturing process provide protection in the event of unforeseen problems. In addition, in a compliant cGMP process and facility:

- "*Drug and medical device companies must have procedures in place for the investigation of process deviations and product failures*" (see e.g., 21 C.F.R. §§ 211.100 (b), 211.192 (drugs))
- "*Because continuous improvement is necessary to maintain current good practices, the ability to recognize repeated errors and downward shifts in product quality also is very important. Companies of all types frequently establish internal control limits based on statistical evaluations of their process capability. Such limits are within tolerances set in official or customer specifications and are useful in recognizing potential problems*" (Schwemer, 1998).

It is therefore expected that cGMP compliant manufacturers, who are required to produce medicines of high quality, should have controls in place to foresee problems such that they can assure safety & efficacy every day, every dose.

2.2.3 Basic Intent of cGMP is to Minimize Risk to Patients

The basic intent of cGMP is to minimize the risks involved in any pharmaceutical manufacturing operation that cannot be eliminated through testing the final product. Since it is impossible to test 100% of the products, following cGMP thus reduces the risk of a defective or adulterated product appearing on the pharmacy shelf. cGMP covers all aspects of production; from starting materials, facilities, equipment, training, controlling changes and investigation of deviations. The crux of cGMPs is that quality has to be built into the product by taking care of how the product is made. One cannot just test quality into the product. If the product is not made according to the exact method prescribed in the NDA or ANDA, and variability is not controlled and managed, one cannot guarantee the quality of the product. Tests of final products are designed only for known impurities. But, change in manufacturing conditions can generate unknown and harmful impurities which will never be detected by the standard final product acceptance tests.

That is why adherence to the cGMP regulations assures the identity, strength, quality, and purity of drug products, and manufacturers of medications are required to adequately control their manufacturing operations. This includes establishing strong quality management systems, obtaining appropriate quality raw materials, establishing robust operating procedures, detecting and investigating product quality deviations, and maintaining reliable testing laboratories. This formal system of controls at a pharmaceutical company, if adequately put into practice, helps to prevent

instances of contamination, mix-ups, deviations, failures, errors and defective products. This assures that the manufactured drug products meet their quality standards.

2.3 cGMP Regulations – Finished Pharmaceuticals – Application to Drug Products, Drug Substances, Excipients, Containers/ Closures

"CGMPs provide for systems that assure proper design, monitoring, and control of manufacturing processes and facilities. Adherence to the CGMP regulations assures the identity, strength, quality, and purity of drug products by requiring that manufacturers of medications adequately control manufacturing operations" (FDA, Facts About the Current Good Manufacturing Practices (CGMPs)). Therefore, to assure the *identity, strength, quality and purity of the drug products*, all processes and equipment manufacturing a medicinal product in a cGMP operation should be made stable and reduced to low levels of defects, i.e., made capable. It is the responsibility of the manufacturer therefore to ensure that the process used to manufacture a drug product for sale in the U.S. market is stable and capable.

Above we stated that because of changing conditions along the life cycle of start-up processes, rigid monitoring and controls must be put in place to develop the quality history of the process. The sampling, monitoring and controls provide protection in the event of *unforeseen problems*. "*Drug and medical device companies must have procedures in place for the investigation of process deviations and product failures*" (see e.g., 21 C.F.R. §§ 211.100 (b), 211.192 (drugs)). "*Because continuous improvement is necessary to maintain current good practices, the ability to recognize repeated errors and downward shifts in product quality also is very important. Companies of all types frequently establish internal control limits based on statistical evaluations of their process capability. Such limits are within tolerances set in official or customer specifications and are useful in recognizing potential problems*" (Schwemer, 1998). It is therefore expected that cGMP compliant manufacturers, who are required to produce medicines of high quality, should have controls in place to foresee problems such that they can assure safety & efficacy every day, every dose.

There are manufacturers who have very advanced and modern quality systems in place to manage the above. The FDA could incentivize those manufacturers by giving them more freedom with implementing process and equipment changes. This will enable the FDA to focus its limited resources on manufacturers who do not meet such high standards.

2.4 Understanding GMPs

cGMP is a Process-Oriented Regulation

The main issue behind those who complain about the cGMP regulation and/or are unable to follow cGMP comes from their lack of understanding of what cGMP really is. Unfortunately, many of those who claim to be cGMP experts and so-called consultants or trainers also lack the fundamental understanding of cGMP and keep propagating a wrong view of cGMP. These people fail to look at cGMP as a regulation which focuses on the technology, processes and/or practices used in production, rather than only on documentation and analytical methods and analysis of the output. Since manufacturing processes, equipment and other conditions are variable due to sometimes unforeseen circumstances, the focus on following cGMP should be to ensure that the variability is under-

Index