ICH Q10 IMPACT DETERMINATION: ANALYSIS OF PHARMACEUTICAL QUALITY SYSTEM ENABLER IMPLEMENTATION PRIOR TO AND AFTER THE RELEASE OF THE ICH Q10 GUIDANCE DOCUMENT

by

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(Under the Direction of Michael Bartlett)

ABSTRACT

According to 21 Code of Federal Regulation (CFR) Parts 210 & 211, pharmaceutical product manufacturers must establish and follow current good manufacturing practices (cGMP) to produce quality products while meeting regulatory standards. However, the rate of advancements in manufacturing science and the pharmaceutical industries increasing understanding of quality systems greatly outpaced the updates to the cGMP regulations. Regulatory authorities began to work on initiatives intended to provide the means for meeting cGMP regulation requirements with modern Pharmaceutical Quality Systems (PQS). One such initiative is the International Council for Harmonization (ICH) "Q10 Pharmaceutical Quality Systems" guidance. This research project was performed to test the hypothesis that the ICH Q10 guidance document aided pharmaceutical manufactures and resulted in improvements to their PQS. Statistically significant differences were determined in PQS enabler implementation, suggesting ICH Q10 had a positive impact on PQS development.

INDEX WORDS: US Food and Drug Administration, The International Council for Harmonization, Good Manufacturing Practices, Pharmaceutical Quality Systems, ICH Q10

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B.S., The University of Georgia, 2020

A Thesis Submitted to the Graduate Faculty of The University of Georgia in Partial Fulfillment of the Requirements for the Degree

MASTER OF SCIENCE

ATHENS, GEORGIA

2021

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May 2021

DEDICATION

To all those who inspired curiosity and a love of learning in me. Without each of you, I would never have made it to the culmination of this journey.

ACKNOWLEDGEMENTS

I would like to thank my major advisor Dr. Michael Bartlett for his mentorship and for giving me the opportunity to discover the intricacies of regulatory science through research. I would also like to thank Dr. Gurvinder Rekhi and Dr. Michael Fulford for their guidance and support in completing this thesis. Additionally, I would like to thank the faculty of the International Biomedical Regulatory Affairs program for preparing me to become a professional in Regulatory Science and Affairs, as well as Dr. Wided Missaoui for her dedication to her students and for always advocating on behalf of us. Last but not least, I would like to thank my family and friends for supporting me throughout this journey.

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CHAPTER 1

INTRODUCTION

1.1 Purpose of Research

The recent advancements in manufacturing science and increasing understanding of the positive impact of quality systems has brought about the need of guidance for industry on appropriate implementation and maintenance practices for PQS. This need is currently being addressed by regulatory body projects, such as the United States Food and Drug Administration's (FDA) Pharmaceutical cGMPs for the 21st Century Initiative[1]. Additionally, international harmonization efforts have been made towards this need, as seen by the ICH and International Organization for Standardization (ISO) guidance documents related to PQS. The purpose of this research is to determine if the ICH "Q10 Pharmaceutical Quality Systems" guidance document had a statistically significant positive impact on the PQS of manufacturing sites around the world. This was determined by the evaluation of the degree of difference in production principles and observable behavior between manufacturing sites prior to ICH Q10 publication and sites after ICH Q10 publication using data from the St. Gallen OPEX Data Benchmarking Questionnaire database.

1.2 Problem Statement

Despite the numerous initiatives and guidances, a review of the overall trends in FDA 483 observations and warning letters reveals that cGMP issues, particularly inadequacies that should be addressed by a complete and effective PQS, continue to be the most frequent infraction. Examples of the most frequent observations include quality control procedures not in

writing or not fully followed for drug products and lack of or inadequate CAPAS procedures for device products[2]. Therefore, more work must be done by both the pharmaceutical industry and the regulatory agencies to mitigate the continuing violations. An insight into the effectiveness of past and current projects will allow for the use of the more effective methods and a reevaluation of the less effective methods. Understanding the impact of ICH Q10 and analyzing the PQS elements that were positively influenced will facilitate this insight and identify areas for further improvement.

1.3 Outcomes of Research

This research evaluates the responses to the St. Gallen OPEX Benchmarking Questionnaire, which consists of a number of questions regarding enablers from pharmaceutical manufacturing sites around the world. This study determines the statistical significance and degree of difference in the means of the before ICH Q10 and after ICH Q10 analysis group. Furthermore, this study evaluates the statistical significance and degree of difference in the means of each of the five enabler categories, as defined by the St. Gallen OPEX group. Overall, the identification and analysis of the impact of ICH Q10 provides insight into the effectiveness of this guidance document in improving pharmaceutical manufacturing site quality systems to produce more safe and effective products.

CHAPTER 2

BACKGROUND

2.1 Quality in the Pharmaceutical Industry

Due to the nature of pharmaceutical products, it is of utmost importance to maintain quality in all aspects of their manufacture. The quality of these products can be evaluated through the combination of the products established identity, strength, purity, and other quality characteristics, which are designed to ensure the required levels of safety and effectiveness[3]. The approach to achieve this is a system of programs, policies, processes, and facilities that ensure quality. This system is known today as the Pharmaceutical Quality System (PQS). This idea is based on the premise that quality should be built into the product as in many cases testing alone cannot be relied on to ensure product quality[4]. However, effectively and efficiently implementing PQS principles is not a simple task. Therefore, both national regulatory bodies and international groups have done tremendous work on developing regulations and guidances to facilitate the quality of pharmaceutical products.

2.2 History of Pharmaceutical Quality Systems Regulations and Guidances

An example of these efforts to facilitate quality in pharmaceutical products are the FDA's current good manufacturing practices (cGMP) regulations, 2l CFR parts 210 and 211, which establish, and mandate appropriate behaviors, processes and resources be in place. As discussed earlier, these regulations are intended so that pharmaceutical manufactures can produce pharmaceutical products with a reasonable expectation of and ability to ensure quality. These regulations are part of a living document and has gone through several evolutions as

technology and industry experience has advanced. One of these evolutions was the major update made effective on December 18, 1978[3]. This update codified cGMP requirements for devices in 21 CFR part 820. One of the new requirements introduced in this update was that device manufacturers must establish and follow quality systems to help ensure that their products consistently meet applicable requirements and specifications. Another major update was initiated by the FDA in 1990. This update, which would not be put into effect until June 1, 1997, had two primary goals. The first goal was to incorporate the design controls authorized by the Safe Medical Devices Act into the part 820 cGMP regulations. The second goal was the harmonization of cGMP regulations with the requirements for quality systems contained in international standards. The harmonization effort was focused on two main international standards, created by the International Organization for Standards (ISO), ISO 9001:1994 "Quality Systems--Model for Quality Assurance in Design, Development, Production, Installation, and Servicing" and ISO committee draft 13485 "Quality Systems--Medical Devices--Supplementary Requirements to ISO 9001". Although these updates were the first steps towards PQSs as they are known today, the rate of advancements in manufacturing science and the pharmaceutical industries understanding of quality systems greatly outpaced the updates to the cGMP. Recognizing this, the FDA began the Pharmaceutical cGMPs for the 21st Century Initiative in August of 2002. This initiative entailed the integration of quality systems and risk management approaches into the FDA's existing programs[5]. The goal of this work was to encourage the industry to adopt modern and innovative manufacturing technologies as well as provide the means for meeting cGMP regulation requirements with modern PQSs. An added benefit of this initiative was the resulting harmonization with both international regulatory systems and the FDA's own medical device quality systems regulations.

A more recent PQS related guidance from the FDA was the “Guidance for Industry Quality Systems Approach to Pharmaceutical cGMP Regulations” published in October of 2006[6]. This guidance shares many similarities with the ICH Q10 guidance. The first of these being that they were both intended to help manufacturers in implementing modern quality systems and risk management approaches to meet the requirements of the FDA's cGMP regulations. Furthermore, both of these guidances describe a comprehensive PQS model. This guidance can be seen as the preliminary phase of the eventual adoption of the ICH “Q10 Pharmaceutical Quality Systems” guidance.

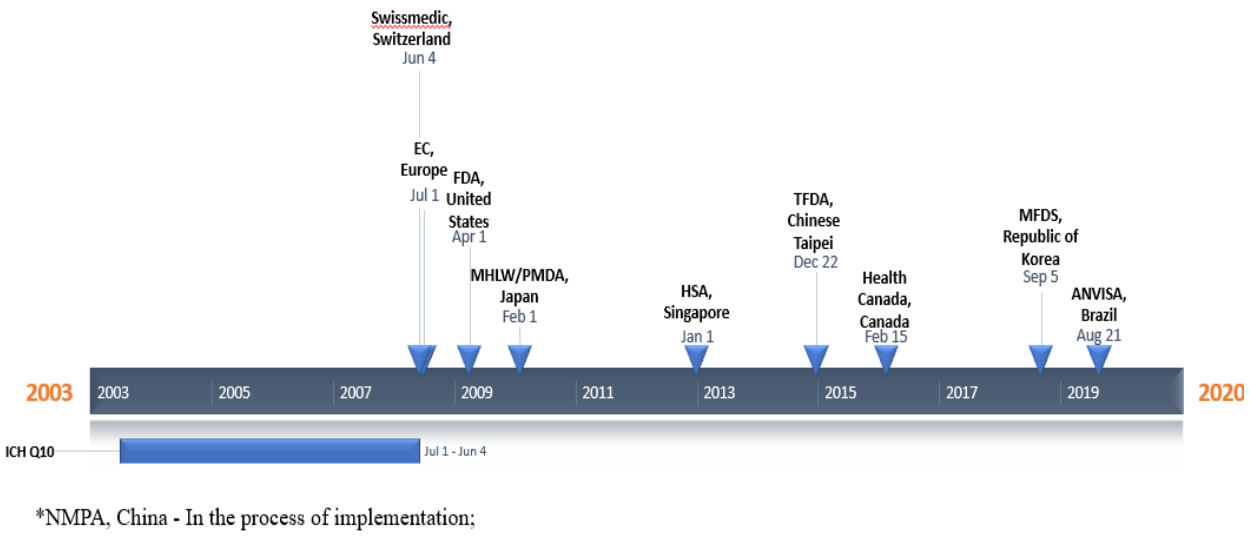
2.3 Description If ICH Q10 Pharmaceutical Quality Systems

As discussed thus far, the U.S. Food and Drug Administration (FDA) and other national organizations are acutely aware of the importance of pharmaceutical quality and have taken measures to ensure and promote quality. One of these measures is the International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use (ICH). This project assembles the regulatory authorities of Europe, Japan and the United States as well as experts from the pharmaceutical industry of these three different regions. These groups then collaborate for discussions of the scientific and technical aspects of pharmaceutical product registration. An objective of the ICH is to develop guidelines on the quality, safety, and efficacy of pharmaceutical products. These guidelines are subsequently adopted by ICH regulatory members and observers resulting in international harmonization.

The ICH “Q10 Pharmaceutical Quality Systems” is an essential guidance document for pharmaceutical manufacturers attempting to develop systems to ensure the quality of their products. This document was finalized in June of 2008 and was later implemented by the

European Commission in July of 2008 and the FDA in April of 2009. A full visualization of the implementation history of ICH Q10 is presented in figure 1.

Figure 1



[7]

While ICH Q10 does include applicable cGMP regulations, it is not intended to create any new expectations beyond the current regulatory requirements. Rather, the intended purpose is to assist pharmaceutical manufacturers in designing and implementing an effective quality management system. ICH Q10 attempts to fulfil this purpose by detailing a model pharmaceutical quality system (PQS), also referred to as the ICH Q10 model. This model is centered on International Organization for Standardization (ISO) quality concepts and can be implemented during the product lifecycle's different stages. An effective PQS is described in ICH Q10 Section 3.1.3 as a system that "assures that the desired product quality is routinely met, suitable process performance is achieved, the set of controls are appropriate, improvement opportunities are identified and evaluated, and the body of knowledge is continually expanded."[7].

The elements of an effective PQS, as described in the ICH Q10 guidance are as follows: Management Responsibilities, CAPA system, Process Performance and Product Quality Monitoring System, Change Management System, and Management Review[7]. In addition to these elements, ICH Q10 emphasizes the importance of and interconnectedness of Knowledge Management and Quality Risk Management to a successful and effective PQS, which are both further described in the sister guidance documents ICH "Q8 Pharmaceutical Development" and ICH Q9 "Quality Risk Management" respectively. The CAPA systems of the manufacturing sites captured through the St. Gallen OPEX benchmarking questionnaire are evaluated using metrics such as the number of CAPAs as well as a calculated "Supplier Reliability Score"[8]. As such, these values were not compatible with the analysis performed and will be excluded from this study. Additionally, while Knowledge Management and Quality Risk Management are relevant to the implementation and interpretation of ICH Q10, no conclusion will be drawn to the effectiveness of these guidances to maintain a clear and concise scope for the study.

Management Responsibilities

The ICH Q10 model provides details on management responsibilities that are critical to the performance of the PQS. These management duties should be conducted to oversee and continually improve the pharmaceutical quality system. The cornerstone of the management responsibilities is the management commitment, as senior management has the ultimate task of ensuring that an effective PQS is in place to achieve the quality objectives of the organization. These tasks not only involve management participation in the design, implementation, and maintenance of the PQS, but also defining the roles and authorities of any needed organizational units related to the PQS[7].

Management is also responsible for leading the direction of the organization's quality approach, which can be accomplished through the establishment of a quality policy and subsequent quality objectives. The Q10 guidance advises that senior management establish a quality policy so that the overall intentions and directions of the organization related to quality are described and visible[7]. To support the quality policy, quality objectives aligned with the organization's strategy must be described and communicated to the relevant personnel. These objectives can then be used as benchmarks for the evaluation of progress towards fulfilment of the quality policy.

Two common activities in the pharmaceutical industry are outsourcing and acquisitions, and both of these activities also have associated management responsibilities described in the ICH Q10 guidance. Acquisitions result in the change of product ownership, thus necessitating clear communication on the responsibilities of each party and the transfer of requisite information. These necessities are to be ensured by management because the process can be very complex. In regard to outsourcing, pharmaceutical companies are ultimately responsible for the activities or products of the vendor due to the GMPs of 21 CFR 211 subpart E3[9]. Therefore, management is responsible for ensuring processes are in place to guarantee the control of outsourced activities and quality of purchased materials.

Lastly, typical management responsibilities are also described in this guidance. These duties are resource management, internal communication, and management review. Resource management is defined as the determination of what resources are needed for a given process or activity and the subsequent provision of these resources[7]. It also is important to ensure that the resources are being utilized appropriately and effectively. Internal communication involves the establishment of appropriate communication processes. These communication processes allow

for the flow of appropriate information between levels and units of the organization. They are also the pathway for product quality or PQS issue escalation. Management review is a responsibility of senior management which allows for continued improvement and sustained suitability of both the manufacturing processes and the PQS[7]. It is also identified as one of the four enhanced PQS elements of the ICH Q10 model and will be discussed further in the evaluation of these PQS elements.

Process Performance and Product Quality Monitoring System.

The Process Performance and Product Quality Monitoring System elements allows the PQS to maintain a state of control. In order to achieve this, the effective monitoring system must both provide assurance of the continued capability of the process and identify areas for continual improvement. One of the responsibilities of this system is developing the data management and statistical tools for measurement and analysis of parameters and attributes identified in the control strategy. Another responsibility is the gathering of feedback on product quality from both internal and external sources for enhancement of process understanding. The implementation of a Process Performance and Product Quality Monitoring System has useful impacts on all the product lifecycle stages. An example of this is the application of this system on the pharmaceutical development stage, where the information generated throughout development can be used to establish a control strategy for manufacturing processes[7].

Change Management System

An effective change management system enables the organization to evaluate, approve, and implement changes appropriately. One of the key activities of this system are the use of subject matter experts and diverse teams to contribute to the evaluation of the proposed changes. Another is the monitoring and evaluation of the change after it is implemented, which allows for

the determination of whether change objectives were achieved and if there were any harmful impacts on product quality[7]. It is these activities, as well as others, that allow change management systems to implement changes that facilitate continual improvement and assure that there are no unintended consequences of these changes.

Management Review

The last PQS element enhanced by the ICH Q10 model is management review of process performance and product quality. The review should include the results of regulatory inspections, audits, and periodic quality reviews. The periodic quality reviews allow for evaluation of the other systems, such as the effectiveness of process and product changes originating from the CAPA system and the findings of the process performance and product quality monitoring system. Some of the actions that management review is responsible for are improving the manufacturing processes and the reallocation of resources to better fit the process[7]. Additionally, this management review has the important role of capturing and distributing pertinent information. Through these activities, this system works as the head of the PQS to provide assurance that process performance and product quality are managed over the lifecycle of the product.

2.4 Description of the St. Gallen OPEX Benchmarking Program

The St. Gallen OPEX Benchmarking Program was initiated in 2004 as an international research project to examine the link between the performance scores and the enablers leading to this performance. Their research program involves the collection of both Key Performance Indicators (KPIs) and responses to the enabler questionnaire. The questionnaire data is composed of the responses to a number of questions regarding enablers from pharmaceutical manufacturing sites around the world. Enablers are defined by St. Gallen as “production principles (methods &

tools but also observable behavior). The values show the degree of implementation based on a self-assessment on a 5-point Likert scale."[8]. These enablers are divided into the following 5 categories: Total Productive Maintenance (TPM), Total Quality Management (TQM), Just-in-Time (JIT), Effective Management System (EMS), and Basic Elements (BE).

Total Productive Maintenance

TPM is a comprehensive approach to equipment maintenance that emphasizes proactive and preventative maintenance. The goal of this program is to maximize the operational efficiency of equipment. This can be achieved through the TPM model, consisting of the 5S foundation and its eight supporting pillars. The 5S foundation includes Sorting, Setting in Order, Shining, Standardizing, and Sustaining the work environment. The eight supporting pillars are focused on proactive and preventative techniques for improving equipment reliability. These activities include Autonomous Maintenance, Planned Maintenance, Quality Maintenance, Focused Improvement, Early Equipment Management, Training and Education, Safety/Health Environment, and TPM in Administration[10].

This group is further divided into three sub-categories in the St. Gallen Enabler Questionnaire, Preventative Maintenance, Housekeeping, and Effective Technology Usage, all designed to evaluate methods that ensure a high level of equipment stability and availability[11]. Examples of questions for each of these sub-categories are presented below:

Preventative Maintenance: "D02 - Maintenance plans and checklists are posted closely to our machines and maintenance jobs are documented."[8]

Housekeeping: "D16 - Our plant procedures emphasize putting all tools and fixtures in their place."[8]

Effective Technology Usage: “D10 - We are constantly screening the market for new production technology and assess new technology concerning its technical and financial benefit.”[8]

This Enabler Category does not have a direct comparison to any specific ICH Q10 PQS Elements as it is a manufacturing philosophy. However, it does include some aspects that are covered by management review through its identification of unsuitable working environments or behaviors.

Total Quality Management

The overarching objective of TQM is to reduce process variability and thereby increase process stability[11]. Some of the TQM techniques to improve operational performance include scientific methods for work organization, monitoring, and value analysis of work processes[12]. These techniques are advocated by the leading authorities of TQM due to the numerous benefits that they offer [13]. These benefits include the identification of the points of highest leverage for quality improvement, the continuous evaluation of alternative solutions to diagnosed problems and the full and detailed documentation of the results obtained after changes are implemented [12 13]. All of these benefits are useful in the pursuit of continuous improvement and ultimately the reduction in process variability.

The TQM enabler category is comprised of assessments of necessary practices to stabilize the manufacturing equipment as well as to ensure robust supporting processes[11]. Examples of such practices include process management techniques and integration of the relevant stakeholders (suppliers, customers, and the R&D department). This enabler category is composed of the following four sub-categories: Process Management, Customer Integration, Cross-Functional Product Development, and Supplier Quality Management. Each of these

subcategories contribute towards the reduction of process variability. Examples of questions for each of these sub-categories are presented below:

Process Management: "E04 - In our company there are dedicated process owners who are responsible for planning, management, and improvement of their processes." [8]

Cross-Functional Product Development: "E09 - Manufacturing engineers (e.g. Industrial engineers) are involved to a great extent in the development of a new drug formulation and the development of the necessary production processes."[8]

Customer Integration: "E15 - Our customers frequently give us feedback on quality and delivery performance."[8]

Supplier Quality Management: "E21 - We rank our suppliers, therefore we conduct supplier qualifications and audits."[8]

Just-In-Time

JIT production is a manufacturing philosophy that originates from the Japanese based Toyota company. The objective of JIT is to establish an advantage through the delivery of superior products or services in terms of both cost and quality[14]. This objective can be achieved through the pursuit of several specific goals, those being the continual elimination of waste, improvement of product quality, and maximization of production efficiency. In order to realize these goals, JIT relies on the utilization of the concept of added value in its analysis of products. Added value aids in the determination of value-adding processes, which are desirable and should be optimized, and non-value-adding processes, which are wasteful and should be minimized or eliminated. The benefits that arise from the JIT management philosophy are improved product quality, increased process efficiency and reduction of cost. However, there are some limitations which include certain prerequisites to implementation, increased dependence on

the consistency of supply chains, and the loss of the buffer against supply/demand fluctuations associated with safety stocks or excess capacity[14].

The OPEX benchmarking group describes the prerequisites to JIT implementation in the following quote "Only after both equipment and processes are stabilized, can Just-In-Time (JIT) production potentially be achieved within a production environment."[11]. This is because in order to reduce the unnecessary work-in-progress inventory and minimize cycle times, JIT is reliant on robust processes. Without robust processes, the increased stress placed on the production system and lack of safety stocks to compensate for operational instabilities can result in product delivery disruptions and even shortages of important pharmaceutical products[11].

The JIT enabler category is broken into four sub-categories. These sub-categories are Set-Up Time Reduction, Pull Production, Layout Optimization, and Planning Adherence. Examples of questions for each of these sub-categories are presented below:

Set-Up Time Reduction: "F01 - We are continuously working to lower set-up and cleaning times in our plant."[8]

Pull Production: "F07 - Our production schedule is designed to allow for catching up, due to production stoppings because of problems (e.g. quality problems)."[8]

Layout Optimization: "F15 - Our processes are located close together so that material handling and part storage are minimized."[8]

Planning Adherence: "F24 - We usually meet our production plans every day."[8]

Effective Management System

The EMS enabler category was designed to assess the management systems and capabilities of the manufacturing sites. The objective of EMS is described by Friedli and co-editors in their book *Leading Pharmaceutical Operational Excellence* as "to motivate and align

employees to work for a common goal"[15]. Important contributors to this objective are the involvement of all employees and active contribution towards continuous improvement. Additionally, the management team must define, communicate and support the objectives for the manufacturing site[11].

The EMS enabler category contains four sub-categories. These being Direction Setting, Management Commitment and Company Culture, Employee Involvement and Continuous Improvement, and lastly, Functional Integration and Qualification. Examples of questions for each of these sub-categories are presented below:

Direction Setting: "G01 - Our site has an exposed site vision and strategy that is closely related to our corporate mission statement."[8]

Management Commitment and Company Culture: "G07 - Site management (committee) empowers employees to continuously improve the processes and to reduce failure and scrap rates."[8]

Employee Involvement and Continuous Improvement: "G17 - We have implemented tools and methods to deploy a continuous improvement process."[8]

Functional Integration and Qualification: "G28 - Each of our employees within our work teams (in case workers are organized as teams) is cross-trained so that they can fill-in for others when necessary."[8]

Basic Elements

The BE enabler category is defined by the St. Gallen OPEX group as representing "a collection of practices that are shared by all three technical categories (TPM, TQM and JIT), including the implementation of fundamental OPEX practices such as Standardization and Visual Management" [11].

The BE enabler category is divided into two sub-categories. The first is Standardization and Simplification. The second is Visual Management. Examples of questions from both of these sub-categories are presented below.

Standardization and Simplification: "H01 - We emphasize standardization as a strategy for continuously improving our processes, machines and products."[8]

Visual Management: "H07 - Performance charts at each of our production processes (e.g. packaging) indicate the annual performance objectives."[8]

A comparison of the ICH Q10 PQS elements and the associated St. Galen Enabler group is presented in Figure 2.

Figure 2 ICH Q10 PQS Elements and St. Gallen OPEX Benchmarking Enabler Categories comparison

ICH Q10 PQS Elements	St. Gallen OPEX Benchmarking Enabler Categories
No direct comparison as it is a manufacturing philosophy. Some principles are covered by **Management Review** since this would include improving the manufacturing processes.	**TPM** (Preventative Maintenance, Housekeeping, Effective Technology Usage)
Process Performance and Product Quality Monitoring System	**TQM** (Process Management, Customer Integration, Cross-functional Product Development, Supplier Quality Management)
No direct comparison as it is a manufacturing philosophy. Some principles are covered by **Management Review** since this includes reallocation of resources to better fit the process	**JIT** (Set-up Time Reductions, Pull System, Planning Adherence, Layout Optimization)
Management Responsibilities	**EMS** (Direction Setting, Management Commitment & Quality Culture, Employee Involvement & Continuous Improvement, Functional Integration and Qualification)
Change Management System	**BE** (Standardization and Simplification, Visual Management)

CHAPTER 3

METHODS, RESULTS, AND DISCUSSION

3.1 Methods

This study involved the analysis of the results from 358 responses to the St. Galen OPEX benchmarking questionnaire, related to more than 330 pharmaceutical manufacturing sites (2003 – 2018) [11]. This data was obtained through collaboration with the Operational Excellence team of the Institute of Technology Management at the University of St. Gallen (ITEM-HSG). The database consisted of the 1-5 Likert scale responses to the survey questions regarding enablers. The total responses for all enablers before 2009 were combined into one data set and the same was done for the responses from 2009 and later. This data was then transferred from the excel sheets into the Stata statistics software for comparison using histograms to visualize the spread, determining the summary statistics of the sets, and performing statistical tests. Further analysis was performed using these same techniques on subsets of the samples to analyze if significant differences can be observed at the enabler category level. Additionally, the mean, median and standard deviation were determined for the responses from each year. This was performed to determine if there was an overall trend of improvement overtime for the PQSs represented in the sample, which could be an alternative explanation for any observed statistically significant difference between the Pre-09 and Post-09 groups.

The statistical tests that were performed include a two-sample t-test assuming unequal variances, a two-sample z-test and the Wilcoxon signed rank test. The z-test and t-test were performed to determine whether the means for enabler response of these two groups, before 2009

and after 2009, are equal. Therefore, the tests will be performed as two-tailed tests. The results of these tests would allow us to identify if there is a statistically significant difference between the means of the group, as well as which group has the higher value. The Wilcoxon signed rank tests was performed in addition to the t-test as it is an alternative for this test when the distribution of the differences between the two samples cannot be assumed to be normally distributed. This test is a comparison of means between the samples and would allow us to confirm if there is a statistically significant change in mean from the pre-2009 group to the post-09 group. For all tests, a significance level of $\alpha = 0.05$ was used.

This comparison was also performed on subsets of the total group to analyze if the measured change observed at the combined level occurs at the enabler category level.

3.2 Complete Population Results

The summary statistics of the complete population analysis groups are presented in Table 1.

Table 1 Complete Population Summary Statistics

GROUP	# OF OBSERVATIONS	MEAN	MEDIAN	STANDARD DEVIATION
BEFORE 2009	16,840	3.297	3	1.268
AFTER 2009	19,492	3.409	4	1.264

The after 2009 group had a sample mean of all question responses 0.112873 greater than the before 2009 sample group. This mean difference is supported by the results of the statistical tests, presented in Table 2.

Table 2 Complete Population Statistical Test Results

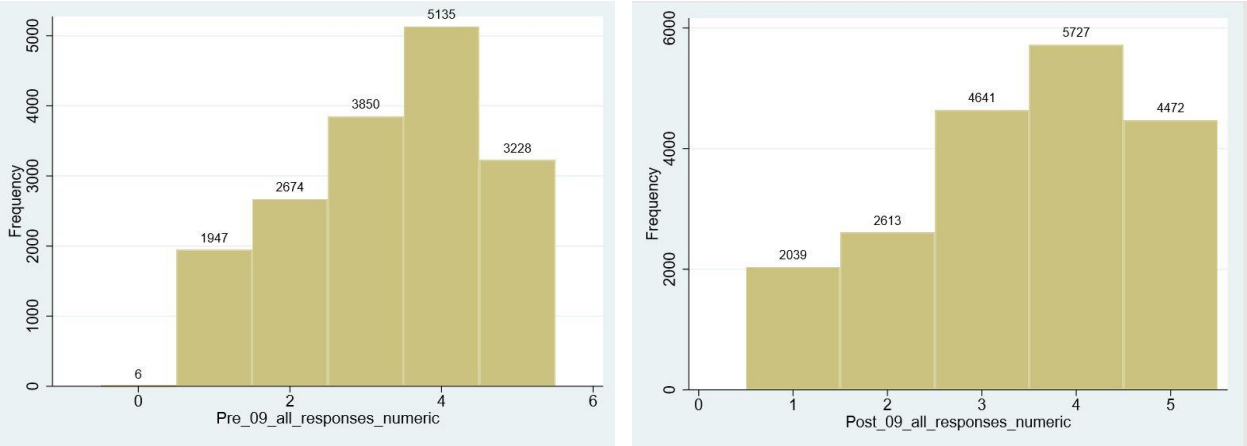
GROUP	P-VALUE OF T-TEST	P-VALUE OF Z-TEST	P-VALUE OF WILCOXON TEST	T SCORE OF T TEST	Z SCORE OF Z TEST	Z SCORE OF WILCOXON TEST
BEFORE 2009 VS AFTER 2009	< 0.0000	< 0.0000	< 0.0000	8.4754, d.f.: 35532.7	10.729	8.987

*Df are Satterwhite's degrees of freedom calculated by Stata.

Based on these results we can reject the null hypotheses of the t and z tests that the means of the two groups are equal and conclude that the observed 0.113 difference is statistically significant. Furthermore, we can reject the null hypothesis of the Wilcoxon signed-rank test that the means of the two groups are equal and conclude that the observed difference in mean is statistically significant.

Figure 3 presents histograms of all responses from both the before 2009 and after 2009 groups for the purpose of visualizing the observed changes. This figure shows the increased proportion of responses scored as five and the decreased proportion of responses scored as one or two. This suggests that observed differences are a result of more complete enabler implementation.

Figure 3 Pre 09 & Post 09 complete population histogram comparison



3.3 Enabler Category Results

The summary statistics of the enabler category analysis groups are presented in table 3.

Table 3 Enabler Category Summary Statistics

GROUP	# OF OBSERVATIONS	MEAN	MEDIAN	STANDARD DEVIATION
BEFORE 2009 TQM	3,827	3.299	4	1.280
AFTER 2009 TQM	4,033	3.591	4	1.298
BEFORE 2009 TPM	2,971	3.333	4	1.305
AFTER 2009 TPM	2,662	3.359	4	1.242
BEFORE 2009 JIT	3,735	3.004	3	1.264
AFTER 2009 JIT	4,214	3.086	3	1.277
BEFORE 2009 BE	2,288	3.315	4	1.254
AFTER 2009 BE	3,578	3.495	4	1.240
BEFORE 2009 EMS	3,590	3.663	4	1.099
AFTER 2009 EMS	4,548	3.651	4	1.095

The Total Quality Management (TQM) enabler category had a 0.292 difference in mean. The Total Productive Maintenance (TPM) enabler category had a 0.026 difference in mean. The Just-In-Time (JIT) enabler category had a 0.0826 difference in mean. The Basic Elements (BE) enabler category had a 0.181 difference in mean. Lastly, the Effective Management System (EMS) enabler category had a 0.013 difference in mean. The results of the statistical analysis are presented in Table 4.

Table 4 Enabler Category Statistical Test Results

GROUP	P-VALUE OF T-TEST	P-VALUE OF Z-TEST	P-VALUE OF WILCOXON TEST	T SCORE OF T TEST	Z SCORE OF Z TEST	Z SCORE OF WILCOXON TEST
TQM	< 0.0000	< 0.0000	< 0.0000	10.0418, d.f. 7846.42	12.937	9.126
TPM	0.4455	0.3317	0.0003	0.7631, d.f. 5610.25	0.971	3.651
JIT	0.0039	0.0003	0.0408	2.8834, d.f. 7850.35	3.662	2.046
BE	< 0.0000	< 0.0000	0.2719	5.4020, d.f. 4832.61	6.745	1.099
EMS	0.6066	0.572	0.5803	0.5150, d.f. 7692.72	0.565	0.553

*Df are Satterwhite's degrees of freedom calculated by Stata.

Based on these results we can reject the null hypotheses of the t and z tests that the means of the two TQM analysis groups are equal and conclude that the observed 0.292 difference in means is statistically significant. Furthermore, we can reject the null hypothesis of the Wilcoxon signed-rank test that the means of the two groups are equal and conclude that the observed difference in mean is statistically significant.

Based on these results we fail to reject the null hypotheses of the t and z tests that the means of the two TPM analysis groups are equal and conclude that the observed is 0.026 difference in means difference is not statistically significant. However, we can reject the null

hypothesis of the Wilcoxon signed-rank test that the means of the two groups are equal and conclude that there is a statistically significant difference in mean.

Based on these results we can reject the null hypotheses of the t and z tests that the means of the two JIT analysis groups are equal and conclude that the observed 0.083 difference in means is statistically significant. Additionally, we can reject the null hypothesis of the Wilcoxon signed-rank test that the means of the two groups are equal and conclude that there is a statistically significant difference in mean.

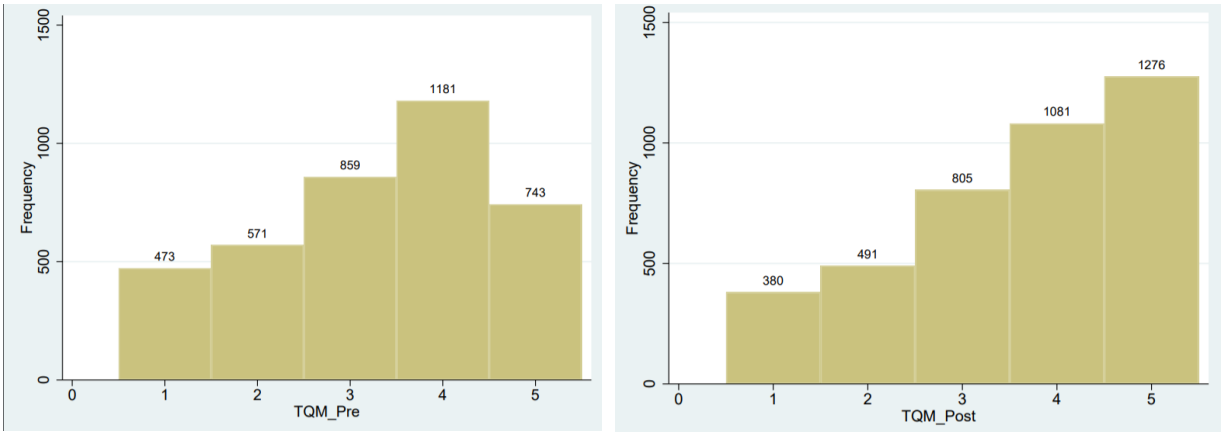
Based on these results we can reject the null hypotheses of the t and z tests that the means of the two BE analysis groups are equal and conclude that the observed 0.181 difference in means is statistically significant. We fail to reject the null hypothesis of the Wilcoxon signed-rank test that the means of the two groups are equal and conclude that there is not a statistically significant difference in mean between these BE groups.

Based on these results we fail to reject the null hypotheses of the t and z tests that the means of the two EMS analysis groups are equal and conclude that the observed 0.013 difference is not statistically significant. Furthermore, we fail to reject the null hypothesis of the Wilcoxon signed-rank test that the means of the two groups are equal and conclude that there is not a statistically significant difference in mean between these groups.

Figure 4 compares histograms of the before 2009 TQM and after 2009 TQM enabler category analysis groups, for the purpose of visualizing the observed changes. The histograms show a large increase in the proportion of response scored as five and a slight decrease in the responses scored as one through four. This suggests that complete enabler implementation for this category greatly increased and partial enabler implementation was less frequent after the

release of the ICH Q10 guidance. It is likely that the trends observed in the complete population results are largely due to the effects of the TQM enabler category.

Figure 4 Pre 09 & Post 09 TQM Enabler Category histogram comparison



3.4 Analysis by Year

The mean, median and number of observations for all responses from each year that responses were provided are presented in Table 5 below.

Table 5 Yearly Analysis Data

YEAR	MEAN	MEDIAN	# OF OBSERVATIONS
2003	3.288	4	8958
2005	3.303	3	1916
2006	3.247	3	482
2007	3.169	3	2342
2008	3.426	4	2807
2009	3.382	4	2692
2010	3.362	4	1727
2011	3.573	4	1350
2012	3.453	4	2585
2013	3.258	3	1593
2014	3.320	3	5251
2015	3.417	4	2448
2016	3.411	4	2899
2017	3.740	4	1340
2018	3.403	4	544

This data is visualized in Figures 5 and 6, which consist of line graphs of the means and medians vs the year, respectively.

Figure 5 Complete Population Mean Vs. Year Line Graph

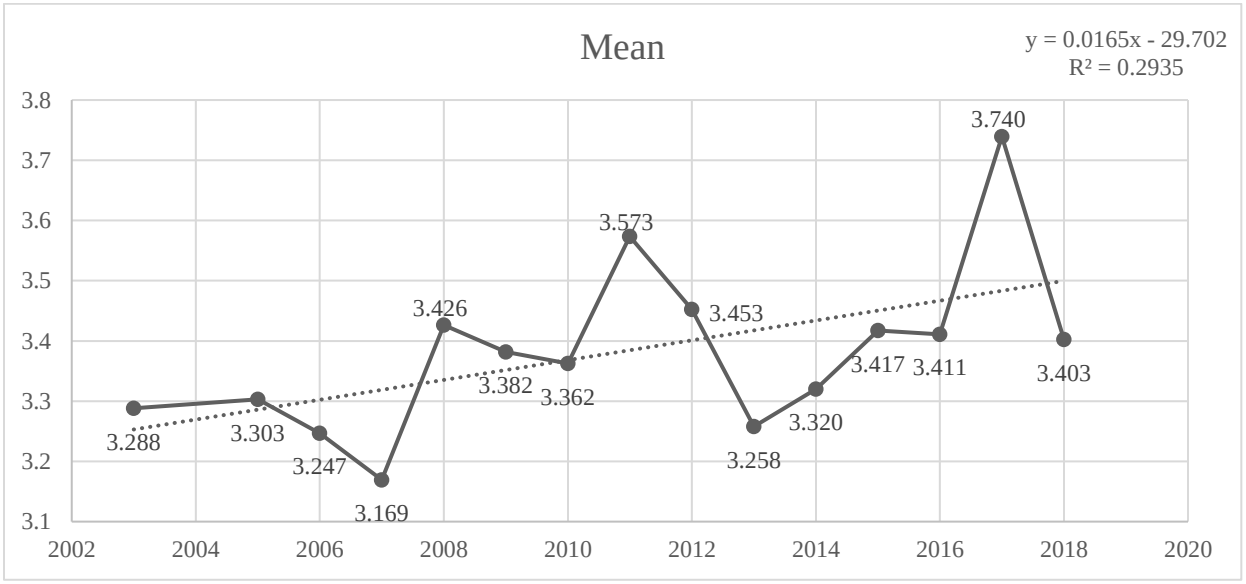
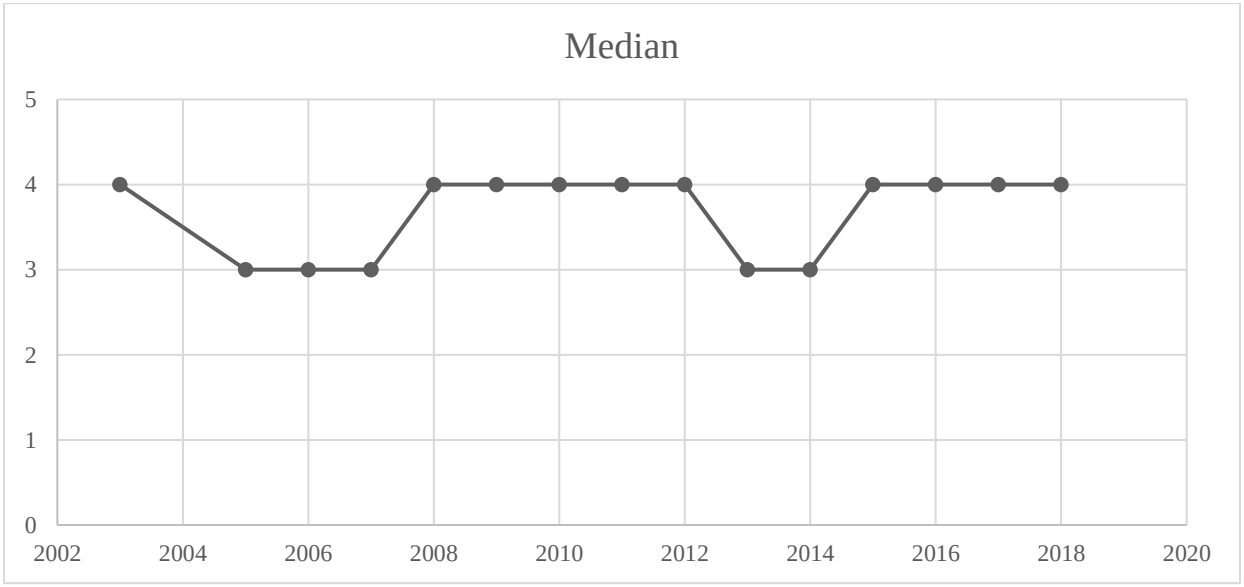


Figure 6 Complete Population Median Vs. Year Line Graph



3.5 Discussion

Assessment of Complete Population

This research project was performed to test the hypothesis that the ICH Q10 guidance document aided pharmaceutical manufactures and resulted in improvements to their PQS. Due to the statistically significant differences that were determined in PQS enabler implementation across all enabler categories in the complete population analysis, we propose that ICH Q10 had a positive impact on PQS development and maintenance. The test results confirm an increase in mean of all enabler question responses, which is evidence of the population of manufacturing sites in this sample having a greater degree of PQS enabler implementation after the release of the ICH Q10 guidance document. This increase is a result of increasing percentage of responses scored as five and decreasing percentage of responses scored as one or two between the Pre-09 and Post-09 groups, as visualized in figure 1.

The yearly analysis of the complete population supports the findings that the mean and median of the enabler implementation responses is greater after 2009 than they were before 2009. The lowest mean before 2009 occurred in 2007 with a value of 3.169 and the highest mean occurred in 2008 with a value of 3.426. This increase from 2007 to 2008 represents the second largest increase between years. After 2009, the lowest mean occurred in 2013 with a value of 3.258 and the highest mean occurred in 2017 at value of 3.740. These mean minimums are reflected in the trends of the medians, which generally held at 4 but dipped to 3 from 2005 to 2007 and from 2013 to 2014. The large degree in variability from year to year for the means suggests that changes in enabler implementation are not solely attributed to quality improvement over time, if at all. In particular, the peak in 2011 is followed by two years of decreasing means

and several more years of relatively similar means. The large degree of difference in the number of observations in each year is a limitation to this analysis.

Assessment of Enabler Categories

While the complete population results indicate that the ICH Q10 guidance was effective, the further analysis at the enabler category level is essential to determining the impact of ICH Q10 on various PQS elements. This analysis provides insight into the most effective components of ICH Q10 as well as identification of potential areas for further improvement.

Two enabler categories, TQM and JIT, were determined to have a statistically significant difference in mean between the before 2009 and after 2009 analysis groups by all tests. The Total Quality Management enabler category displayed the largest difference in mean of all the enabler categories, at a difference of 0.292 compared to the 0.113 difference observed for the complete population. This suggests that TQM enabler implementation improved the most from the release of the ICH Q10 guidance document. Therefore, the ICH Q10 PQS element that can be identified to have been the most effective is Process Performance and Product Quality Monitoring System.

The other enabler category that was determined to have significant differences in mean by all tests, Just-In-Time, does not have an ICH Q10 PQS element that can be directly associated with it. However, some aspects of JIT can be attributed to activities performed under the Management Review element. This PQS element is responsible for improving the manufacturing processes and the reallocation of resources to better fit the process, based on the review of regulatory inspections, audits, and periodic quality reviews[7]. These responsibilities coincide with the JIT's specific goals of continual elimination of waste, improvement of product quality, and maximization of production efficiency. Furthermore, the JIT enabler subcategories Layout

Optimization and Planning Adherence can be directly improved through the Management Review Process. Therefore, our results suggest that the Management Review ICH 10 PQS element was an effective part of the ICH Q10 guidance as a whole and contributed to the observed improvement in JIT enabler implementation.

In addition to the two enabler categories that were determined to have statistically significant differences in mean by all tests, two enabler categories were determined to have a statistically significant difference in mean by one test result and not the other. These split results suggest that the observed difference is not a strongly significant and could indicate that some of the test assumptions were not met. These enabler categories are BE and TPM. The BE enabler category includes a collection of practices that are shared by all three technical categories (TPM, TQM and JIT) [11]. These practices include the implementation of fundamental OPEX practices like Standardization and Simplification, as well as Visual Management. The implementation of these practices is guided by the Change Management PQS element under the ICH Q10 PQS model. Therefore, the effectiveness of the Change Management portion of the ICH Q10 guidance document can be evaluated through the changes in the BE enabler category. For this enabler category, the difference in means between the two sample groups was found to be 0.181 and this difference was determined to be statistically significant by both the Z and T tests. However, the Wilcoxon Sign Rank test determined there was not a statistically significant difference. Based on these results we believe that the Change Management PQS element was an effective part of the ICH Q10 document and contributed to the observed increase in BE enabler implementation.

TPM is a comprehensive approach to equipment maintenance that emphasizes proactive and preventative maintenance[10]. The TPM enabler category is designed to evaluate methods that ensure a high level of equipment stability and availability, which is reflected by the three

subcategories Preventative Maintenance, Housekeeping, and Effective Technology Usage[11]. Although TPM is a manufacturing philosophy and there is no direct comparison to any of the ICH Q10 PQS elements, there are some enablers in this category that could be covered by Management Review as this includes improving the manufacturing processes. This supports the Management Review ICH 10 PQS element being an effective part of the ICH Q10 guidance, as well as contributing to the observed improvement in TPM enabler implementation.

Lastly, the EMS enabler category was found to not have a statistically significant difference in mean between the prior to 2009 and after 2009 sample groups. Additionally, this enabler category is the only one that showed a decrease in mean from before the ICH Q10 release to after its release. The EMS enabler category was designed to assess the management systems and capabilities of the manufacturing sites. Therefore, it can be reasonably associated with the Management Responsibilities ICH Q10 PQS element. Based on the statistical test results, it appears that the Management Responsibilities was not effective in improving EMS enabler implementation. This suggests that this PQS element was not effectively described in the ICH Q10 guidance document.

3.6 Conclusion

This study determines if the ICH “Q10 Pharmaceutical Quality Systems” guidance document has had a statistically significant positive impact on the PQS of manufacturing sites around the world. This was determined by the evaluation of the degree of difference in production principles and observable behavior between manufacturing sites prior to ICH Q10 publication and sites after ICH Q10 publication using data from the St. Gallen OPEX Data Benchmarking Questionnaire database. Additionally, this study assesses the statistical significance and degree of difference in the means of each of the five enabler categories.

These enabler categories are linked to associated ICH Q10 PQS elements, and the effectiveness of these elements are evaluated.

The results from this study demonstrate that the manufacturing sites studied showed a greater degree of PQS enabler implementation after the release of the ICH Q10 guidance document. Furthermore, 4 of the 5 enabler categories displayed some degree of statistically significant difference in measures of central tendency. These results suggest that the Management Review, Change Management System and Process Performance and Product Quality Monitoring System ICH Q10 PQS elements were all effectively described in the guidance and implemented by the manufacturing sites. However, the EMS enabler category showed a decrease in mean enabler score, which suggests the Management Responsibilities ICH Q10 PQS element was not effectively described or implemented.

cGMP issues and inadequacies that can be addressed by an effective PQS continue to be observed by regulatory authorities and thus continued work by industry and regulators is required. This work can be aided by the insight into the effectiveness of the ICH Q10 guidance provided by this study. Overall, ICH Q10 appears to have been effective, as well as most of its individual PQS elements but clarifying and promoting the implementation of the Management Responsibilities is an area of improvement that can be focused on.

References

1. U.S Food and Drug Administration. Pharmaceutical cGMPs for the 21st Century - A Risk-Based Approach Final Report. In: Services DoHaH, ed., September 27, 2004.

2. Damron C. FDA 483 Observations and Warning Letter Trends: Crowell & Moring, 2019.

3. Center for Devices and Radiological Health (CDRH). Quality System (QS) Regulation/Medical Device Good Manufacturing Practices. 2018 09/27/2018. https://www.fda.gov/medical-devices/postmarket-requirements-devices/quality-system-qs-regulationmedical-device-good-manufacturing-practices (accessed 02/06/21).

4. International Conference on Harmonisation. ICH Q8 PHARMACEUTICAL DEVELOPMENT. 2009

5. U.S Food and Drug Administration. PHARMACEUTICAL CGMPS FOR THE 21ST CENTURY — A RISK-BASED APPROACH FINAL REPORT, 2004.

6. US Food and Drug Administration. Guidance for Industry: Quality Systems Approach to Pharmaceutical CGMP Regulations. In: U.S. Department of Health and Human Services, ed., 2006.

7. International Conference on Harmonisation. ICH Q10 PHARMACEUTICAL QUALITY SYSTEM, 2008.

8. Friedli T, Koehler S, Buess P, Basu P, Calnan N. *FDA Quality Metrics Research Final Report Year 1*, 2017.

9. 21CFR211 Subpart E. In: DEPARTMENT OF HEALTH AND HUMAN SERVICES, ed. 4, 2020.

10. Vorne. TPM (Total Productive Maintenance). 2019. https://www.leanproduction.com/tpm.html.

11. Friedli T, Koehler S, Buess P, Eich S, Basu P, Calnan N. *FDA Quality Metrics Research Final Report Year 2*, 2018.

12. García-Bernal J, Ramírez-Alesón M. Why and How TQM Leads to Performance Improvements. Quality Management Journal 2015;**22(**3):23-37 doi: 10.1080/10686967.2015.11918439[published Online First: Epub Date]|.

13. Hackman JR, Wageman R. Total Quality Management: Empirical, Conceptual, and Practical Issues. Administrative Science Quarterly 1995;**40**(2):309-42 doi: 10.2307/2393640[published Online First: Epub Date]|.

14. Cheng TC, Podolsky S. *Just-in-Time Manufacturing: An introduction*: Springer Netherlands, 1996.

15. Friedli T, Basu P, Bellm D, Werani J, editors. *Leading Pharmaceutical Operational Excellence*. 1 ed: Springer-Verlag Berlin Heidelberg, 2013.