IMPACT ASSESSMENT OF THE QUALITY SYSTEM REGULATIONS FOR MEDICAL DEVICES - ISO 13485.2003 AND 21 CFR 820 AND THE CAPA SYSTEM

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(Under the Direction of Randall Tackett)

ABSTRACT

In the medical device industry product quality, safety, identity and effectiveness are of utmost concern. Processes, equipment and personnel drive product quality, and together ensure safe and effective product is produced meeting quality characteristics defined by the company and industry. In an ideal medical device environment there would be no errors, but it is not ideal and errors can occur. Medical device companies follow regulatory documents and policies which provide guidance to correct, prevent and resolve errors. A Corrective and Preventive Action (CAPA) System can be established to monitor and track errors. Two regulatory documents provide guidance for a CAPA system: FDA regulation 21 CFR 820 – Quality System Regulation and ISO Standard 13485:2003 – Medical Devices: Quality Management Systems—Requirements for Regulatory Purposes. These documents provide the framework for handling errors, enforcing and documenting corrective/ preventive actions and tracking. CAPA systems track and ensure actions are taken to remediate errors.

INDEX WORDS:21 CFR 820, ISO 13485:2003, Corrective and Preventive Action, CAPA, medical devices, Quality System Regulation.

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DEDICATION

This thesis is dedicated to my parents, Tony and Rose Ann Whittaker and my sister, Allison Whittaker.

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CHAPTER 1

Introduction

1.1 History of Medical Device Companies

Medical device companies are required by federal regulations to manufacture products that are safe and effective and meet the identity, strength, and purity they claim to have. In order to accomplish this, companies are held to specific standards and regulations that provide guidance and requirements for the manufacture of products. The processes and associated activities are also regulated to ensure consistency in the operation to ensure that medical devices produced meet the quality characteristics defined by the company and are safe and effective for use. One of the regulations for medical devices is the implementation and maintenance of quality systems. Quality control developed from the need for control of product and processes. Peter Drucker believed that if the manufacturing industry simultaneously implemented the four principles of post modern factory – statistical quality control, the new concept of manufacturing accounting, the use of the 'flotilla' organization and the use of the system approach, existing conflicts would be eliminated and a much more efficient factory would be created (Reference #21) . Quality control activities were initiated and prevalent in the 1940s, 1950s, and 1960s. Quality control then evolved over time into an era of quality engineering in the 1970s, and has progressed since then into the emerging field of systems engineering in the 1990s and present day.

1.2 International Organization of Standardization (ISO) Overview

International Organization of Standardization (ISO) is a worldwide association. ISO provides national standards for ensuring that the required characteristics are met for products and operations such as quality, safety and efficiency (Reference #10). Originally developed in 1926 as the International Federation of the National Standardizing Associations (ISA), the organization focused primarily on mechanical engineering. In 1942 during World War II the organization disbanded and was re-organized and redeveloped in 1946 as the current-named organization, ISO. The organization works to prepare International Standards through the assistance of technical committees. Currently there are approximately 2700 technical committees, subcommittees and working groups. ISO currently has more than 17500 international standards in their portfolio, with standards for areas such as agriculture and construction, mechanical engineering, distribution and manufacturing, transport, good management practices and medical devices (References #12 and #13).

ISO 13485 is a standard that was originally published in 1996 and revised in 2003. It represents the minimum requirements for a comprehensive quality management system focused on the design and manufacture of medical devices. The intention of the standard is to establish guidance and standards for medical device companies. This provides a measure for industry to be assessed against to determine their ability to provide medical devices and related services that consistently meet the established requirements and applicable regulatory specifications. ISO 13485:2003 is the most current revision of the document. It replaced the 1996 version of the same document. Prior to ISO13485:1996, there were three other regulatory documents from which ISO 13485 was based upon and eventually replaced, one other ISO document and two European Norm (EN) documents – EN 46001:1997, EN 46002:1997, ISO 13488:1996 (Reference #13). Although this ISO document, 13485, serves as a stand-alone document, it harmonizes with ISO 9001. However, the main difference between the two documents is that

ISO 9001 requires that continual improvement of the organization's overall performance should be a permanent objective of the organization, while ISO 13485 has key objectives that to maximize the probability that a medical device organization will meet regulatory. ISO 9001 provides guidance on various methods such as; improved organizational capabilities, alignment of activities for improvement and the flexibility to react quickly to opportunities which can help to provide continuous system improvement.

1.3 Food and Drug Administration (FDA) Overview

Changes in process and products are also governed by FDA regulations under the Federal Law. The FDA is responsible for regulating many items such as: food, dietary supplements, drugs, vaccines, blood products and medical devices for safety and efficacy. The FDA was initiated in the late 19th century and continuously evolves and changes their regulations and guidances to improve the industries they regulate.

An area that the FDA pays close attention to is quality system regulations (QSR) of product and processes. The FDA document that provides guidance for quality system regulations of medical devices is 21 CFR 820. The Code of Federal Regulation (CFR) is the minimum legal requirements that must be followed. The quality systems for FDA-regulated products are known as current good manufacturing practices (cGMP) (Reference #17). The cGMP requirements for medical devices in part 820 were first authorized by section 520 (f) of the Federal Food, Drug and Cosmetic Act. On July 21, 1978, the FDA issued a final rule using this section of the FDCA to prescribe GMP requirements for all medical devices and on December 18, 1978 the regulation was made effective and coded under Part 820, therefore, becoming Law for follow-up by the Federal Agency during inspections (Reference #17).

Over the next two decades, the FDA revised the cGMPs to harmonize them with the ever-changing medical device industry. Specifically, in 1990, the FDA revised the cGMPs to include design controls, and also looked at making attempts to harmonize the principles of the regulation with the international ISO standards present at the time: ISO 9001:1994 and the draft of ISO 13485. After much revision, the quality system regulation 21 CFR 820 was published on October 7, 1996, and made effective on June 1, 1997.

The Quality System Regulation 21 CFR 820 was written with built in flexibility (Reference #17), so that all medical device manufacturers could adapt the regulations to their operations, process and product. The FDA expects that companies use 21 CFR 820 to establish their company policies and develops a quality system uniquely designed for their operations. Due to the fact that the document was meant to provide regulation for various types of medical devices, 21 CFR 820 prescribes a broad framework to which all medical device manufacturers must follow. The FDA dictates that medical device manufacturers must establish a quality system. When doing this they should use their judgment in applying 21 CFR 820 appropriately and applicably to their process and product while remaining compliant with the regulation.

1.4 Corrective and Preventive Action System

Corrective Action and Preventive Action, known as CAPA is a concept developed within the Good Manufacturing Practices (GMPs). Corrective and Preventive Action is one of the subsystems of Quality Management, as show in Figure 1.1 (Reference #3). Both ISO 13485:2003 and FDA 21 CFR 820 require medical device manufacturers to establish and maintain a CAPA system and both documents detail the requirements for CAPA systems.

FIGURE 1.1 – QUALITY MANAGEMENT SUBSYSTEMS

A CAPA system is used many industries including the medical device industry. Its focus is on the systematic investigation of discrepancies, deviations, and/or failures that occur in the product, processes, equipment or associated areas. A 'healthy' CAPA subsystem includes three provisions that do the following (Reference #3):

- CORRECTION – Identify and correct existing nonconforming product or other quality problems.
- CORRECTIVE ACTION – Identify and eliminate the causes of existing nonconforming product and other quality problems
- PREVENTIVE ACTION – Identify and eliminate the causes of potential nonconforming product and other quality problems

A correction, for example, would be correcting a step in a standard operating procedure, or crossing through and re-writing the results on a data sheet for clarity. Some examples of corrective actions are installing visible and audible alarms on production equipment to detect failures, or malfunctions, and developing a calibration tracking system or installing calibration management software to help manage calibrations within the company, ensure that they are done on time and track that the results meet the specifications. Some examples of preventive

actions include implementing the use of risk assessments, revising change control and document control procedures, and using methods such as Statistical Process Control (SPC) to trend information and detect possible changes or issues. Corrective actions are developed and implemented in an effort to prevent the recurrence of a discrepancy/deviation, while preventive actions are developed and implemented in an effort to prevent the occurrence of a discrepancy/ deviation before it occurs. Therefore, corrective actions are reactive and preventive actions are proactive in a system, implying that corrective actions are implemented after the nonconformity has occurred, whereas preventive actions are implemented prior to the nonconformity occurring.

When establishing a CAPA system, a manufacturer must ensure that their corrective and preventive actions are effective in correcting/ preventing the discrepancy and that they do not adversely impact other aspects of the product, process, equipment or system. This can be done by having a verification process. Such a process would be specific to the issue, but could entail monitoring the corrected error over time, sampling and testing product against the company specifications, testing product-contact equipment if applicable and follow-up/ spot check training of employees involved with the corrective or preventive action. The establishment and implementation of a corrective and preventive action system is required by the regulations for all medical device manufacturers. CAPA is a pivotal element of the overall quality management system.

Why is a CAPA system needed in a medical device manufacturing? Research provides three reasons why a CAPA system is beneficial and needed:

1. Regulatory Requirements – Both FDA and ISO regulations require that a Corrective and Preventive Action System be established and maintained by any company that produces finished medical devices. Therefore, supplying a systemic approach to follow-up, ensure that actions are taken and that they appropriate. When inspected or audited by a regulated body, the

CAPA system can be viewed as a reflection of how well or poorly a company handles errors, implements actions and ensures their appropriateness. The more effective the CAPA system is within the company, one would expect less recalls, investigations and product loss (Reference #18).

2. Good Business Practice – An effective CAPA system will help to reduce and control the financial impact on a company by reducing quality system problems, streamlining improvement and implementing corrective/preventive methods. This can result in increased production, a more efficient process and increased product (Reference #18).

3. Customer Satisfaction – The capability of a company to have a CAPA system that identifies and takes appropriate action to correct existing errors, and effectively implements controls to prevent the occurrence of potential errors can play a role continued customer satisfaction. As a company works towards product/process improvement through corrective/preventive actions, their goal is essentially to supply their customers with a better, safer and more effective product and maintain or even increase customer satisfaction (Reference #18).

1.5 Project Rationale & Literature Review

The purpose of this project is to assess the impact of the FDA regulation 21 CFR 820 and ISO 13485:2003 from a medical device standpoint, focusing specifically on the subparts that provide guidance to the requirements for Corrective Action and Preventive Action. The assessment of the two guidances will compare and contrast the requirements for establishing and maintaining a CAPA system, assess their impact on US medical device companies in industry, and discuss the significance of both regulations and their differences. Industry will be assessed using a questionnaire and all results will be presented in this project. Conclusions will be made to determine the impact of the two regulations on CAPA systems, to evaluate their differences and to determine if one regulation is more significant or widely used than the other and to provide recommendations based on the research and responses.

These regulations and quality systems have become more important to the workforce and more prevalent in industry. Prior research discovered assessments focusing primarily on the Quality Management System using ISO 9001, and Pharmaceutical Quality Systems. These two topics can be considered to be the building blocks for ISO 13485 and Medical Device Quality Systems respectively. The two regulations evaluated in this assessment have both been revised over the years. The most recent revisions are ISO in 2003 and the FDA regulation in 2008. The ISO standard has only been in rotation since 1996 and the FDA regulation since the late 1990s. The medical device regulations and Quality System Management/Regulation are always changing as the industry and devices evolve. These regulations are used both nationally in the US and globally. Research of previous works determined that papers focusing on these two regulations had a global approach, such as “Global Regulation Requirements for Medical Devices” by Sandra Brolin in 2008. Brolin focused on the regulatory requirements for medical devices in Argentina, Brazil, Canada, India, Japan, Mexico, Russia, South Korea, and Taiwan and compared them with the European Union requirements. The findings of this study were as follows: most countries have similar requirements of medical devices and are striving to harmonize with the Global Health Task Force (GHTF) guidelines, quality management systems and risk management systems are in most countries and ISO 13485 and ISO 14971 certifications are required or recommended. The study also determined that the classification of medical devices is usually done in accordance with the European Union (EU) system, FDA system, GHTF guidelines or by catalogue (Reference #19).

Similarly, the book published by Amiram Daniel, Ed Kimmelman, and Kimberly A. Trautman, “The FDA and Worldwide Quality System Requirements Guidebook for Medical Devices”, provides guidance on both the FDA and ISO documents on a whole and provides a comparison of all subparts, including Corrective and Preventive Action. Research of previous worked found one other paper, “The New ISO 13485:2003, Detailed Comparison with FDA Quality System

Regulation and ISO 9001:2000" written by Gallifa & Partner, LLC in Switzerland in 2005. This paper focused on introducing the then new ISO 13485:2003 document and compares it in detail with the FDA 21 CFR 820 and the ISO 9001:2000. This paper also presents two business cases dealing with identification and CAPA issues and addresses them based on ISO 13485:2003 and FDA 21 CFR 820. This paper showed that both ISO 13485:2003 and FDA Quality System Regulations texts are complementary in many respects. It also showed that there is still a lot of room for harmonization of global standards (Reference #20).

CHAPTER 2

The Regulations Overview: 21 CFR 820 & ISO 13485

2.1 FDA Regulation 21 CFR 820

21 Code of Federal Regulations (CFR) Part 820 of the Quality System Regulation addresses medical device manufacturers of finished devices intended for use in humans. This regulation consists of various subparts that define specific requirements for the development of a quality system, maintenance, and overall general scope. The subparts for 21 CFR 820 are as follows:

- Subpart A: General Provisions
    - 820.1 Scope
    - 820.3 Definitions
    - 820.5 Quality System
- Subpart B: Quality System Requirements
    - 820.20 Management Responsibility
    - 820.22 Quality Audit
    - 820.25 Personnel
- Subpart C: Design Controls
    - 820.30 Design Controls
- Subpart D: Document Controls
    - 820.40 Document Controls
- Subpart E: Purchasing Controls
    - 820.50 Purchasing Controls

- Subpart F: Identification and Traceability
    - 820.60 Identification
    - 820.65 Traceability
- Subpart G: Production and Process Controls
    - 820.70 Production and Process Controls
    - 820.72 Inspection, Measuring and Test Equipment
    - 820.75 Process Validation
- Subpart H: Acceptance Activities
    - 820.80 Receiving, In-Process and Finished Device Acceptance
    - 820.86 Acceptance Status
- Subpart I: Nonconforming Production
    - 820.90 Nonconforming Product
- Subpart J: Corrective and Preventive Action
    - 820.100 Corrective and Preventive Action
- Subpart K: Labeling and Packaging Control
    - 820.120 Device Labeling
    - 820.130 Device Packaging
- Subpart L: Handling, Storage, Distribution and Installation
    - 820.140 Handling
    - 820.150 Storage
    - 820.160 Distribution
    - 820.170 Installation

- Subpart M: Records
    - 820.180 General Requirements
    - 820.181 Device Master Record
    - 820.184 Device History Record
    - 820.186 Quality System Record
    - 820.198 Complaint Files
- Subpart N: Servicing
    - 820.200 Servicing
- Subpart O: Statistical Techniques
    - 820.250 Statistical Techniques

The following table explains each of the subparts listed above and the requirements detailed in each subpart as it applies to developing quality systems for medical device companies (Reference #2).

TABLE 2.1 – 21 CFR 820, SUBPART REQUIREMENTS

Subpart	Title	Requirements
A	General Provisions	Provides a general scope for GMPs as it relates to medical device manufacturers who produce finished devices. Dictates general provisions for foreign manufacturers, exemptions, definitions of terms associated with quality system regulation, and a quality system requirement for each manufacture of finished medical devices.
B	Quality System Requirements	Dictates the requirements for management responsibility as it applies to a quality policy, organization, responsibility and authority, resources, management representative and review, quality planning and quality system procedures. Also dictates the requirements for quality audits, personnel and their training on the quality system requirements.
C	Design Controls	Dictates the requirements for each company as it applies to developing procedures to control the design of the device in order to ensure that specified design requirements are met. Also discusses design and development planning, design input, design output, design review, design verification, design validation, design transfer, design changes and the design history file.
D	Document Controls	Dictates the requirements for documents that control all aspects of quality system regulations. Also provides specifications for document approval and distribution, and changes to documents.

TABLE 2.1 – 21 CFR 820, SUBPART REQUIREMENTS

Subpart	Title	Requirements
E	Purchasing Controls	Dictates the requirements for establishing and maintaining procedures for all purchased, received product and services. Details requirements for evaluation of suppliers, contractors and consultants and for purchasing data.
F	Identification and Traceability	Defines the requirements for identifying product during all stages of receipt, production, distribution and installation to prevent mixups. This helps to aid in traceability.
G	Production and Process Controls	Dictates the requirements needed for production and process controls to ensure that the production of the device, the process and all associated parts are controlled. Also provides directives for general requirements, environmental control of conditions, personnel health and cleanliness, contamination control, buildings, equipment control, maintenance schedule, inspection, adjustment, manufacturing material and automated processes. Also provides requirements with regards to controlling inspection, measuring, test equipment, calibration, calibration standards and records. Also defines requirements for process validation, personnel requirements, changes to the process, and all aspects associated with process validation.

TABLE 2.1– 21 CFR 820, SUBPART REQUIREMENTS

Subpart	Title	Requirements
H	Acceptance Activities	Provides requirements for receiving, in-process, and finished devices acceptance. Details information for general, receiving acceptance activities, in-process acceptance activities, final acceptance activities and acceptance records. Also provides requirements for acceptance status of the product to indicate conformance or nonconformance with acceptance criteria.
I	Nonconforming Product	Provides requirements for the control of nonconforming product, nonconformity review and disposition, and for rework.
J	Corrective and Preventive Action	Provides the requirements for establishing and maintaining a corrective and preventive action system and all aspects that are associated with corrective and preventive actions.
K	Labeling and Packaging Control	Provides requirements for device labeling specifically label integrity, labeling inspection, labeling storage, labeling operations and control number. Also details manufacturers' requirements for device packaging.

TABLE 2.1 – 21 CFR 820, SUBPART REQUIREMENTS

Subpart	Title	Requirements
L	Handling, Storage, Distribution and Installation	Provides requirements for handling product to avoid errors, storage of product, receipt from and dispatch to storage areas, and the distribution and release of approved finished devices. Also provides requirements for a device that needs installation and the instructions, procedures, and tests associated with installation.
M	Records	Dictates the requirements needed for maintaining records associated with all aspects of the quality system and its subparts. It dictates requirements for confidentiality, record retention periods, exceptions, the device master record, the device history record, quality system records, and complaint files.
N	Servicing	Details where appropriate the requirements for servicing finished devices and ensuring that the specifications are met. It details the requirements for documenting, developing and maintaining service reports.
O	Statistical Techniques	Details the requirements where appropriate for establishing and maintaining procedures that identify valid statistical techniques required for controlling, verifying acceptability and establishing product and process capability and characteristics. Also details information regarding appropriate sampling plans, and valid statistical rationale.

2.2 ISO 13485:2003

ISO 13485:2003 is the most current version of the standard, which provides a framework for quality management systems specifically for medical device companies. The document is harmonized with ISO 9001, which was developed to provide quality management systems for any company. ISO 13485, like the FDA regulation, is divided into various sections:

- Introduction
    - General
    - Process Approach
    - Relationship with other Standards
    - Compatibility with other Management Systems
- Scope
    - General
    - Application
- Normative References
- Terms and Definitions
- Quality Management System
    - General Requirements
    - Documentation Requirements
- Management Responsibility
    - Management Commitment
    - Customer Focus
    - Quality Policy
    - Planning
    - Responsibility, Authority and Communication
    - Management Review

- Resource Management
    - Provision of Resources
    - Human Resources
    - Infrastructure
    - Work Environment
- Product Realization
    - Planning of Product Realization
    - Customer-related Processes
    - Design and Development
    - Purchasing
    - Production and Service Provision
    - Control of Monitoring and Measuring Devices
- Measurement, Analysis and Improvement
    - General
    - Monitoring and Measurement
    - Control of Nonconforming Product
    - Analysis of Data
    - Improvement

Table 2.2 explains each of the sections listed above for ISO 13485:2003 and the requirements as it applies to developing quality management system for medical device companies (Reference #4).

TABLE 2.2 - ISO 13485:2003 REQUIREMENTS

Section	Requirement
Introduction	This section provides a general overall introduction to the standard and what it dictates with regard to quality management systems, process based approaches, the relationship of the document to ISO 9001and ISO 14969, and the compatibility of the document with other management systems such as environmental management, occupational health and safety management and financial management.
Scope	This section starts by providing a general overview of the standard as it relates to medical devices. It also provides requirements for the application of the standard by medical device manufacturers and an overview of the responsibilities for manufacturers.
Normative References	This section provides ISO 900:2000 as a reference document for ISO 13485:2003.
Terms and Definitions	This section provides all terms and definitions required for the application of this standard. It describes the supply chain understood by ISO 13485.
Quality Management System	This section provides specific detail on the quality management system. It starts by providing the duties of the organization; it details the documentation requirements for a quality management system such as a quality manual and the control of documents and records.

TABLE 2.2 - ISO 13485:2003 REQUIREMENTS

Section	Requirement
Management Responsibility	This section details the requirements for management commitment and their responsibilities. It also details customer focus as it relates to top management. It provides the duties of top management as it relates to the quality policy of the company. This section also details the planning requirements for a quality management system, the requirements of top management as it relates to their responsibility, authority and communication of information. The section also provides the requirements for management review as it relates to review input and output.
Resource Management	This section provides requirements for the resources needed to establish and maintain a quality management system, for human resources requirements such as awareness, competence and training, for infrastructure requirements to achieve conformity to product specifications, for work environment requirements to achieve conformity as it relates to health, cleanliness and reducing adverse effects on product quality.

TABLE 2.2 - ISO 13485:2003 REQUIREMENTS

Section	Requirement
Product Realization	This section details requirements for developing procedures that establish and maintain planning of product realization. It details the responsibilities of the manufacturer for customer-related processes such as determination of requirements related to the finished product, review of the requirements for the product, and effective customer communication methods. This section of the standard also details the requirements for design and development procedures for planning and control of the product, for the inputs and outputs of the product, for the review of the product, for verification and validation of the product, and for control of the changes. This section also covers the requirements to ensure that purchased product conforms to the product specifications; this includes the purchasing process, information and verification. This section also covers the requirements for control of production and service provisions including installation activities, cleanliness and contamination control, servicing activities and sterile device requirements. This section provides requirements for process validation of the product, processes, sterile devices, identification, traceability and active implantable devices. The section also discusses requirements for customer property, preservation of the product, and procedures for the control of monitoring and measuring devices.

TABLE 2.2 - ISO 13485:2003 REQUIREMENTS

Section	Requirement
Measurement, Analysis and Improvement	This section details the requirements for implementing procedures for monitoring, measuring, analysis and improvement processes to demonstrate and ensure conformity of the product to the product specifications. The section also discusses procedures for internal auditing, monitoring and measurement of processes and product, control of nonconforming product, and analysis of data. The section also details the requirement for improvement as it relates to corrective action and preventive action.

CHAPTER 3

The Regulations & Corrective/Preventive Action

3.1 Corrective Action and Preventive Action (CAPA)

In industry, including the medical device industry, a CAPA system is a systematic process of steps. When the steps are performed correctly and in order they can provide a successful resolution of a discrepancy or prevention of a possible discrepancy. Corrective and Preventive Action consists of a seven step process displayed in Figure 3.1 (Reference #9).

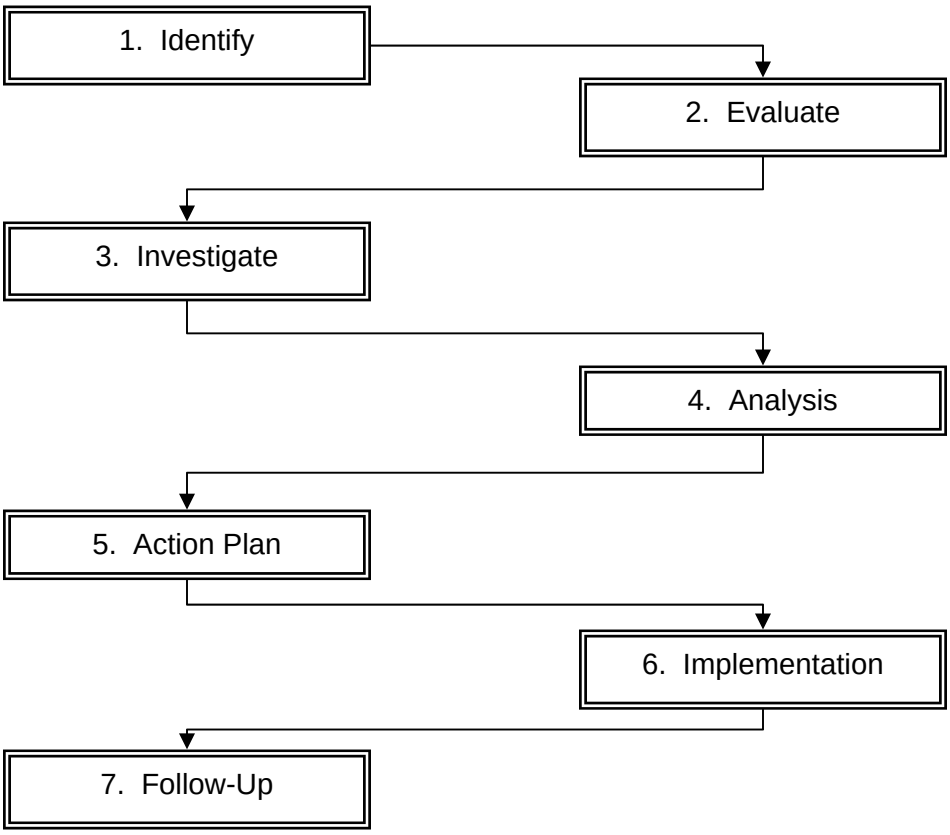

FIGURE 3.1 – SEVEN STEP CAPA PROCESS

Each step is equally important to establishing and maintaining an effective CAPA system. Each step in the process helps to develop, thorough a comprehensive CAPA process, plans to resolve nonconformities (Reference #9). The importance and need of each step in the seven-step process is explained below.

Step 1 – Identify

This step requires the identification of the source of the problem. The source can be one or more forms of documentation such as: service requests, complaints, audit data, trend data or quality inspections. Once a source is identified, the documentation or evidence of the problem needs to be identified and documented. During the identification of the problem or discrepancy there should also be some explanation of the problem (i.e. what it is, specifications or values of failure, time and date, operator, procedures, etc.) All of this information should be documented so that accurate records can be maintained for each discrepancy.

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Step 2 – Evaluation

This step requires that the potential impact of this discrepancy to the company be evaluated. This can include impact to areas such as: costs, process functionality, product quality, safety and customer satisfaction. Once the potential impacted areas are identified, the risk to these areas should to be evaluated. There should be an established scale of risk to determine if it is low, medium, high, or minor, major, critical. Evaluating the risk allows the company to determine if there is some remedial/ immediate action that can be implemented to rectify the discrepancy. In some cases, this remedial/ intermediate correction can satisfactorily and successfully resolve the discrepancy.

Step 3 – Investigation

This investigation step develops a procedure that details how the investigation of the discrepancy will be conducted. This procedure for investigation should focus on the objectives for the action, an investigation summary, and assigned responsibilities and resources. The investigation stage of the CAPA process will investigate the discrepancy in an effort to identify potential root causes. There are various methods used such as failure modes and effects analysis, fault tree analysis and pareto analysis/charts, which can be used to help in the determination of potential root causes. Areas such as: equipment, personnel, training, software, materials, design and external factors will be investigated to determine if they are potential causes of the discrepancy.

Step 4 – Analysis

This step looks to evaluate the data/information collected during the investigation in an effort to analyze it and determine the root cause of the problem. This step utilizes root cause analysis, which can include statistical methodologies and other analysis methods to categorize the potential root causes, and eliminate ones that have little to no impact. Various methods can be used to perform Root Cause Analysis (RCA), some tools used in industry are: Failure Mode and Effects Analysis (FMEA) – a procedure that analyzes the potential failure modes within a system for classification by severity or determination of the effect (Reference #14), Pareto Analysis – a statistical technique that uses the Pareto principle, which in terms of quality improvement states that 80% of the problems are produced by 20% of the key causes (Reference #15), and Fault Tree Analysis (FTA) – a failure analysis which uses a Boolean logic to analyze an undesired state of a system in order to combine a series of lower-level events (Reference #16). These root cause analysis methods also help in the risk mitigation process, which selects controls to reduce and if applicable eliminate the potential recurrence. This can be accomplished in various ways depending on the situation, some examples of risk mitigation are: introducing security/

antivirus software, increased training, introduction of equipment that improves a step or action within the process, specification changes, and a change or improvement in raw materials.

Step 5 – Action Plan

This step determines and defines the best method for corrective/preventive action based on the root cause analysis. A well documented action plan will be developed during this stage. This action plan should include but is not limited to the changes required for correcting and/or preventing the discrepancy, the tasks required for implementing the action and the responsible persons for each task. In order for the action plan to be effective, it must include training of employees and affected personnel on the changes being implemented to correct and/or prevent the discrepancy. For this step to be effective, all aspects of the action plan should be communicated to all involved and affected personnel so as to build awareness and ensure that the situation is corrected according to the documentation.

Step 6 – Implementation

This step involves taking the developed and documented action plan and implementing it to correct the situation. This step will involve the execution of the action plan and the subsequent documentation of all tasks. It is a very important and integral step in the CAPA process as it results in the correction of the discrepancy. All information from the implementation of the action plan is documented and maintained for the company's records.

Step 7 – Follow Up

The last step of the CAPA process is follow up, and is required to verify and assess the effectiveness of the action plan. This step will usually involve some type of verification or validation of the action plan and its implementation and will verify the successful completion of tasks. This step asks key questions to ensure that there are no adverse effects on product,

processes, quality, safety, or service. Examples of possible key questions are: Was training performed with those persons identified as being involved in the change? Are all changes implemented, completed and verified as appropriate? Did the action appropriately correct or prevent the issue? Did the investigation/ verification of the changes provide evidence to show that there was no adverse effect on product/process? The follow-up ensures that the root cause is solved, that proper controls are in place and that adequate monitoring is implemented. The CAPA is closed once the seven steps have been successfully completed. Follow up should also look at the timeframe taken to open, close and complete CAPAs. Evaluating whether or not CAPAs are opened and closed in a timely fashion or if they are prolonged over time, aids in determining the effectiveness of the action implemented and the overall effectiveness of the seven step process used for CAPA.

3.2 CAPA and FDA

The FDA regulation, 21 CFR 820 – Quality System Regulation, uses Section 820.100 to define the requirements for Corrective and preventive action. As stated previously, this section of the regulation requires that each manufacturer of a medical device shall establish and maintain procedures for the implementation of corrective and preventive action. The steps for establishing and maintaining the CAPA system are as follows:

1. Analyzing processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems. Appropriate statistical methodology shall be employed where necessary to detect recurring quality problems.
2. Investigating the cause of nonconformities relating to product, processes and the quality system.

3. Identifying the action(s) needed to correct and prevent recurrence of nonconforming product and other quality problems.
4. Verifying or validating the corrective and preventive action to ensure that such action is effective and does not adversely affect the finished device.
5. Implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems.
6. Ensuring that information related to quality problems or nonconforming product is disseminated to those directly responsible for assuring the quality of such product or the prevention of such problems.
7. Submitting relevant information on the identified quality problems, as well as corrective and preventive actions, for management review.
8. All activities required under this section, and their results, shall be documented.

Each of these steps provided in 21 CFR 820 is very important in assuring that an effective CAPA system is established,

- The first step helps to identify nonconformances, allows for the tracking and trending of data to help evaluate product, process or quality problems and changes over time and to identify deficient areas that may be arising or may have the potential to arise. The application of statistical methodology also allows for evidence to have quantitative information for evaluation and for tracking and trending over time to determine patterns in the process. Therefore, errors can be detected earlier and a company can implement actions sooner, resulting in the correction or prevention of issues that may negatively impact product or the process.
- The second step of investigating all nonconformities allows for the determination of potential root causes to the problem. This process of eliminating all potential causes allows the company to determine all of the possible factors that could have an effect on

the problem, and perform thorough investigations on each to prioritize them by impact, eliminate minor or non-impact causes and determine which identified root cause is the problem.

- The third step allows for the appropriate action to be taken and implemented. It helps a company to decipher whether a correction, corrective action or preventive action needs to be implemented.
- The fourth step provides documented evidence with a high degree of assurance that the corrective and/or preventive action implemented is effective. By using verification and/or validation methods outside testing is performed to ensure that the action was appropriate, to monitor the situation for reduced risk, and that the finished product is still safe and effective.
- The fifth step focuses on the implementation and documentation of methods that are needed to correct or prevent the quality problem. This requirement is important as it allows for the corrective or preventive action to be put in place and fix the nonconformance, but it also allows for any changes to be documented so that all activities and steps can be traced for future audits, tracking and trending, and review.
- The sixth step builds an open line of communication of nonconformances, corrective and preventive actions. This is important in any company as it allows all affected personnel to be knowledgeable of the nonconformance. It helps to build awareness and a sense of ownership and accountability. When persons feel like they are part of the process, and the big picture they are more apt to paying attention, looking for issues, identifying them and assisting in ways to correct and prevent them. This requirement will help to build a strong CAPA system through employees.
- The seventh step is also important because it ensures that the corrective and/or preventive action implemented, the changes to the processes and methods, the root causes, and all other aspects of the problem are approved and acknowledged based

upon their risk level and raised to the appropriate levels within the company. Having management review ensures that all bases are covered, and that all aspects of the nonconformance are done with the company's interest in mind and within the scope of the company's mission and policies.

- The eighth step is a standard practice, documentation of all the results associated with the corrective and preventive action (Reference #2).

CAPA exists as a subsystem within the FDA regulation for Quality System Regulation, as stated in Chapter 1 earlier. This subsystem encompasses four other areas of 21 CFR 820 that are integral in establishing an effective CAPA system.

- 21 CFR 820.90 – Nonconforming Product
- 21 CFR 820.198 – Complaints
- 21 CFR 820.200 – Servicing
- 21 CFR 820.250 – Statistical Techniques

The first subpart 820.90 provides the requirements for establishing procedures for the identification, documentation, evaluation, segregation and disposition of nonconforming product. More specifically, these procedures should be used to define the responsibility for review and the authority for the disposition of nonconforming product, including a process for disposition and review. This is essential for the protection of the company and the consumer. The company ensures that product deemed unsafe or ineffective is not distributed to the consumer, therefore; ensuring that the consumer is not placed in a position to obtain and use nonconforming product. This section also provides justification for use and signature approval of authorized personnel. These procedures will play a role by implementing accountability and traceability in the process, allowing a company to track the product and know who dispositioned it and when and why it was dispositioned. Having these procedures in place also provides a guide for disposition and

prevents early disposition of nonconforming product. Rework procedures if defined and required to remove the defect for nonconforming product must also be established and all activities of rework documented to provide traceability and record retention.

3.3 CAPA and ISO

Although, not as detailed as the FDA regulation, the ISO standard has a developed section for the requirements of a CAPA system. ISO divides the information into two sections – 8.5.2: Corrective Action and 8.5.3: Preventive Action. The first section, 8.5.2, requires that an organization take action to eliminate the cause of nonconformities in order to prevent recurrence. They also require that corrective actions be appropriate to the effects of the nonconformities encountered. Section 8.5.2 requires that a documented procedure for corrective action be established to define requirements for:

1. Reviewing nonconformities, including customer complaints
2. Determining the causes of nonconformities
3. Evaluating the need for action to ensure that nonconformities do not recur
4. Determining and implementing action needed, including, if appropriate, updating documentation
5. Recording of the results of any investigation and of action taken
6. Reviewing the corrective action and its effectiveness.

Although some of the wording is not as specific, the six requirements listed in 8.5.2 of ISO 13485:2003 for the most part mirror the steps provided in 21 CFR 820. The same holds true for the second section, 8.5.3, which provides the requirements for preventive action in ISO 13485:2003. Section 8.5.3 requires that an organization shall determine action to eliminate the causes of potential nonconformities in order to prevent their occurrence. Preventive actions shall be appropriate to the effects of the potential problems. This section (8.5.3) requires that a documented procedure for preventive action be established to define requirements for:

1. Determining potential nonconformities and their causes
2. Evaluating the need for action to prevent occurrence of nonconformities
3. Determining and implementing action needed
4. Recording of the results of any investigations and action taken
5. Reviewing preventive action taken and its effectiveness.

The ISO standard for corrective action identifies six steps for handling a corrective action within an organization, and five steps for handling a preventive action within an organization. The CAPA system works as a sequenced process, in order for it to be an efficient process each step/ requirement should have equal importance, build from the previous one and be performed in order. The process should not move onto the next step/requirement until the previous one has been appropriately satisfied and completed.

- The first requirement provides a process for identifying any nonconformities that occur o or have the potential to occur within the company. It is a broad statement in that it does not identify specific areas to review, which allows a company to make build on this and develop requirements for reviewing specific areas or all areas within their company as appropriate.
- The second requirement for 8.5.2 specifics that the causes of the nonconformities should be determined. For 8.5.3 this is covered in the first requirement.
- The third requirement for 8.5.2 and second requirement for 8.5.3 specifies the need for evaluation of an action to prevent occurrence/recurrence of the nonconformities. The requirement can also facilitate remedial action to performed that may correct the recurrence immediately. Again this requirement does not provide specifics.
- The fourth requirement for 8.5.2 and third requirement for 8.5.3 requires that an appropriate action plan is proposed and implemented and for corrective action where necessary documentation updated to reflect this action plan and implemented changes.

- The fifth requirement for 8.5.2 and fourth requirement for 8.5.3 is an important step in the process. It requires that all aspects of the investigation and action taken be documented. Recording the results is integral because it allows the organization to document all information associated the problem, investigation and implemented action plan. It will also allow for tracking and trending of nonconformities and their respective corrective methods. Recording the results also provides an audit trail for future audits and record review.
- The sixth requirement for 8.5.2 requires that the corrective action and its effectiveness be reviewed. This is important in ensuring that the action plan implemented was appropriate and effective in correcting the nonconformity.

3.4 FDA & ISO Comparison / Contrast

From the requirements for 21 CFR 820 and ISO 13485:2003, both define the compliance requirements for the CAPA system. Both regulatory documents provide a similar framework for tackling nonconformities and improving process/product performance. This assessment aims to evaluate if one document should be or is used more than the other, if the documents should they be used in unison and if one is more helpful in establishing an effective CAPA system. Although similar in their approach, they do possess some differences in their guidance of the recommended steps. Firstly, the FDA regulation is applicable to medical device manufacturers who sell their product in the United States. This includes any foreign device manufacturers who choose to import their devices to the US for sale. The ISO standard however was developed with a more global outlook, and is heavily favored to medical device manufacturers who market their product globally, and ISO 13485 is an international standard recognized worldwide. Another difference between the two standards is certification capabilities. ISO offers a certification process for their members that can be seen as an advantage to globally marketed devices.

The FDA is law, and is not set up in the same way as ISO, therefore; there is no certification system; however, the requirements can impact the approval of shipment in the US for medical device manufacturers through the FDA. One other organizational difference is the setup within the document. The FDA uses one section to define both Corrective Action and Preventive Action; ISO separates them into two distinct subsections within the document. Along with these overall differences in the organizational setup, there are significant contrasts in their requirements for establishing and maintaining procedures for CAPA systems. Table 3.1 and Table 3.2 show the similarities and differences between the two approaches to CAPA systems. (References #2 and #4)

TABLE 3.1 – SIMILARITIES BETWEEN THE TWO REGULATIONS

21 CFR 820	ISO 13485:2003
All manufacturers shall establish and maintain documented procedures for implementing corrective and preventive action.	A documented procedure shall be established to define the requirements for corrective action and preventive action.
Analyze areas to determine existing and potential causes of nonconforming product, or other quality problems. Review areas such as: processes, work operations, concessions, quality audit reports, complaints, service records, quality records, returned product and other sources of quality data.	Reviewing nonconformities (including customer complaints). (8.5.2 Corrective Action)
Investigate the cause of nonconformities relating to product, processes, and the quality system.	Determining the causes of nonconformities. (8.5.2 Corrective Action) Determining potential nonconformities and their causes. (8.5.3 Preventive Action)

TABLE 3.1 – SIMILARITIES BETWEEN THE TWO REGULATIONS

21 CFR 820	ISO 13485:2003
Identifying the action(s) needed to correct and prevent reoccurrence of nonconforming product and other quality problems.	Evaluating the need for action to ensure that nonconformities do not recur. (8.5.2 Corrective Action) Evaluating the need for action to prevent occurrence of nonconformities. (8.5.3 Preventive Action)
Implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems	Determining and implementing action needed, including, if appropriate, updating documentation. (8.5.2 Corrective Action) Determining and implementing action needed. (8.5.3 Preventive Action)
All activities required under this section, and their results, shall be documented.	Recording of the results of any investigation and of action taken. (8.5.2 Corrective Action) Recording of the results of any investigations and of action taken. (8.5.3 Preventive Action)

TABLE 3.2 – DIFFERENCES BETWEEN THE TWO REGULATIONS

21 CFR 820	ISO 13485:2003
Appropriate statistical methodology shall be employed where necessary to detect recurring quality system problems	Not Applicable
Verifying or validating the corrective and preventive action to ensure that such action is effective and does not adversely affect the finished device	Reviewing the corrective action taken and its effectiveness. (8.5.2 Corrective Action) Reviewing the preventive action taken and its effectiveness. (8.5.3 Preventive Action)
Ensuring that information related to quality problems or nonconforming product is disseminated to those directly responsible for assuring the quality of such product or the prevention of such problems	Not applicable
Submitting relevant information on identified quality problems, as well as corrective and preventive actions, for management review.	Not applicable.

From Table 3.,2 it can be seen that ISO 13485:2003 does not place an emphasis on application of statistical analysis to detect recurring quality problems, does not specifically require that verification or validation methods be used to determine effectiveness or ensure safety and quality of the finished device, does not require that the information concerning the corrective/ preventive action be disseminated to the involved personnel and does not place emphasis on the involvement of management in the corrective/ preventive action decisions.

In the medical device industry, these differences are considered quite important. The FDA addresses these areas more than the ISO standard. A company that conforms only to the ISO standard requirements in these areas and not those of the 21 CFR 820 may not sufficiently comply with the FDA requirements. Therefore, a company could be hindered by not having effectively defined procedures for their CAPA system based on these requirements in 21 CFR 820. Why are these differences so important? Statistical methodology, when applied correctly, can provide information on the risk that the quality problem or nonconformity may have to the finished device, process or performance. Guidance for risk management and determination is provided in two documents: ICH Q9 – Quality Risk Management and ISO 14971:2000 – Application of Risk Management to Medical Devices. It can also help to determine how the quality problem started, how long it has occurred, how many times, what areas and can be used to help determine what the best corrective/ preventive methods are as well as assist in the verification/ validation approach. Verification and validation is heavily weighted by the FDA. They require that all processes, changes, equipment, etc. be verified or validated to provide documented evidence with a high degree of assurance that the processes, changes, equipment are effective, safe, meet the requirements of the company and do not adversely effect the finished device. Ensuring that the information is disseminated to the affected personnel speaks for itself. It is an effective way to build awareness, instill accountability and improve performance. If employees are trained on what went wrong, how corrective action was taken, what their part is in assuring that the correction is maintained and how to spot it if it occurs again, then the overall process will improve and in turn help reduce recurrence or generation of similar incidences. Lastly, submitting all the relevant information associated with the corrective and preventive actions for management review is something that the FDA emphasizes, as it provides assurance that the corrective and preventive actions defined and implemented comply with the requirements of the nonconformity and the company's established quality policies and objectives.

CHAPTER 4

Real World CAPA System Application

4.1 Assessment in Industry

In order to assess the Corrective and Preventive Action requirements of the two regulations and their impact on the medical device industry today, various companies were identified, selected and interviewed. The companies were questioned on 21 CFR 820, Quality System Regulation, ISO 13485:2003, Medical Devices-Quality Management Systems-Requirements for Regulatory Purposes, the company's CAPA system and how the two regulations and their CAPA system are impacted by each other in the company structure. The interview questionnaire also examined the CAPA system of each company in terms of effectiveness and improvements for their product and/or process. The questions were categorized based on the steps provided in the two regulatory documents. They focus specifically on the company's CAPA system, what parts of the regulatory documents they have implemented such as management review, verification/ validation of the corrective actions; the questionnaire was developed based on the requirements for a CAPA system detailed in the two regulatory documents. The questionnaire was also developed from input by the industry and university personnel who have experience with CAPA systems and Quality System Regulation. The questionnaire was validated by evaluating each response across the five companies.

The companies evaluated for this project were all located in the State of Georgia, and are all medical device companies with various backgrounds and product lines. Table 4.1 displays the companies and some basic information on each company. The companies evaluated with the questionnaire were chosen based on the following criteria: medical devices companies, location and accessibility, knowledge of persons within the company for easy communication, and the type of device manufactured.

TABLE 4.1 – COMPANIES ASSESSED WITH QUESTIONNAIRE

Company	Location
CIBA Vision Corporation (Global)	Duluth, GA
CryoLife, Incorporated	Kennesaw, GA
CR Bard, Inc (Urology)	Covington, GA
Aderans Research Institute	Marietta, GA
CIBA Vision (Atlanta)	Duluth, GA

4.2 Interview Process

The interview process began with identifying the responsible person within the selected companies who managed and controlled their CAPA system. If there was no such person available, a person closely involved with the CAPA system was chosen. Once identified, the interview questionnaire was provided to the contact with a two-week deadline to complete and return. The companies were informed that all information/ responses provided in the questionnaires would remain confidential, and shall be used only for the purpose of this thesis project and not for outside distribution.

Upon collection of the questionnaires, the information from each company was compared and tabulated, conclusions and recommendations to be made on the impact of 21 CFR 820 and ISO 13485:2003 on the CAPA system and the relationship and effective of all three areas. All information will be taken ‘as-is’ from the questionnaires and each questionnaire will be attached in Appendix 1. To maintain confidentiality the companies will be identified by numbers. The following tables present the information gathered from the questionnaires.

TABLE 4.2 – GENERAL COMPANY INFORMATION

Feature	Company 1	Company 2	Company 3	Company 4	Company 5
Contact's Position	Quality Team Leader	Sr. Quality Systems Engineer	Director, Quality Services	Sr. Compliance Specialist	Quality Assurance Technician
Company Lifespan	20 or more years	20 or more years	20 or more years	20 or more years	6-10 years
Class of Device	II and III	I and II	III	II and III	II
Implantable	No	A few	Yes	No	No
Device Purpose	Vision correction	Gastroenterology	Heart valves and surgical adhesives	Vision correction and promote healthy eyes	Cell delivery system

4.3 Questionnaire Results

TABLE 4.3 – GENERAL RESULTS ON FDA, ISO & CAPA

Feature/ Question	Company 1	Company 2	Company 3	Company 4	Company 5
Which regulation is used?	Both	Both	Both	Both	Both
ISO certified?	Yes	Yes	Yes	Yes	No
CAPA procedures in place?	Yes	Yes	Yes	Yes	Yes
Documented CAPA system	Yes	Yes	Yes	Yes	Yes
Maintain CAPA Records?	Yes	Yes	Yes	Yes	Yes
How long are records maintained?	Minimum of 3 years, but kept longer	At least 7 years	Forever Archived	Record retention policy determines time	Yes indefinitely
Possess a validated tracking database for your CAPA system?	Yes	Yes	Yes	Yes	No
Is one regulation followed more than the other?	No	Used equally	N/A	No	FDA more specific than ISO
Is CAPA approach similar / different?	Similar	Similar	Similar	Similar for medical devices	Similar
Is your application effective?	Yes	Yes	Yes	Yes	No
Do your procedures govern: - follow-up investigation/ effectiveness - tracking and trending of CAPAs - Management review - investigation of root causes	Yes	Yes	Yes	Yes	Yes

All of the identified companies use both of the regulations, and have utilized them in establishing and maintaining procedures and records for a CAPA system. Also of importance, they have a validated tracking database for their CAPA system, except for Company 5. This is important for two reasons. Having a validated database provides a high degree of assurance that they are accurately and satisfactorily capable of tracking and trending their CAPAs which can help them to make decisions on the type, number, action plans, and resolutions of their corrective and preventive actions. Secondly, having a validated tracking database for their CAPA system allows them to have a controlled document that captures any/all changes made to the database over time. If something is added, revised or removed from the database a revalidation would have to occur and those changes documented and approved before implementation.

Although each company had a different definition of a CAPA system they all had the same underlying meaning. Company 2, defines a CAPA system as the requirements of the two standards. Company 3, defines it as the program by which they investigate, document and trend corrective and preventive actions, Company 5 defines the CAPA system as a system to prevent the onset or recurrence of nonconformities, defects or other undesirable situations, Company 1 defines it as a system that has the following Corrective Action is an action to eliminate the causes and reoccurrence of detected nonconformities and other quality related issues, and Preventive Action is an action to eliminate the potential cause and occurrence of nonconformities and other quality issues. Company 4 defines a CAPA system as the set of procedures and processes required to implement and execute the requirements of the CAPA regulations.

It was also noticed that CAPA systems were primarily oriented more for systemic issues. Other corrective actions for all remediation for deviations are handled under CAPA if designated by Management. If the deviation is considered a critical failure, such as final product or packaging,

or if discovered during a vital part of the process such as: process validation, auditing, product development, packaging or postmarket surveillance. Company 4 also states that during the redesign of their CAPA system a risk-based approach to handling nonconformances and deviations requiring corrective and preventive actions. Company 5 also identified that they handle specific deviations under nonconformance reports.

Each company has a similar approach for applying ISO and FDA regulations to their CAPA system. They all stated that they utilize the compliance requirements as defined in 21 CFR 820 and ISO 13485:2003, and ensure that all components are covered and that their CAPA system is compliant. Company 4 stated that they evaluated the two regulatory documents when they developed their CAPA system in addition to evaluating their internal requirements when the procedure was written. Their CAPA system is also evaluated by external auditors for compliance to the two regulations. Company 3 also stated that every year they audit their program to ensure that it is still on track with the requirements. This is an effective method that allows a company to introduce improvement in their CAPA system.

Each company was also asked what criteria was used to open a CAPA. Company 1 and Company 5 opened a CAPA for any of the following reasons: component/ product failure, process/procedure failure, overdue calibration/equipment failure, internal compliance or supplier audits, third party inspection, investigation complaint, field reports and management reviews, validations, supplier performance, postmarket, product development and quality system elements. Company 2 uses a CAPA Determination Form or Preliminary Assessment before initiating a CAPA, and Company 3 bases it on the recognition to take action to correct/ prevent a situation which can result in product or process deviations. Company 4 did not provide specifics on their criteria used to open a CAPA, but stated that the documents they refer to as CAPA are

the highest risk occurrences for their company, and there is specific criteria defined in their procedure.

CAPA systems need to be effective; if they are not effective the benefits of process/ product improvement from appropriate corrective/preventive actions can be negligible or non-existent. All of the companies except for Company 5 viewed their CAPA system and application of the regulations as being effective. Company 2 claimed that their CAPA system has proven to be a systemic methodology to identify root causes, corrective and preventive actions and verify effectiveness. Similarly Company 3 stated that in order for them to maintain their product approvals and certification, effectiveness had to be prevalent, and that their actions frequently addressed the root of the problem and prevented reoccurrence. Company 1 also stated that there has been greater emphasis placed on improving effectiveness the CAPA system. Company 4 states that their recent inspections have not resulting in findings against their CAPA system and they will be making tweaks to their CAPA system to provide a smoother functionality for users. Company 5 is a newer company in comparison to the other companies. They are still in developing their CAPA system. They are trying to build more control into their system and felt that it was not effective. Company 5 also felt that their CAPA system lacked accountability of assigned responsibilities and tracking of CAPA factors such as length of time open, and actions taken to date.

A CAPA system cannot be considered effective if there are no methods to measure effectiveness. Effectiveness can be evaluated by monitoring the number of CAPAs corrected on the first occurrence, the number of corrective actions versus the number of preventive actions, CAPA first time through (FTT) systems, corrective versus preventive action ratios, and repeat/ recurrence methods such as the Paynter charts. Whether a company chooses to use one or multiple methods they need to ensure that they have something in place that it is up-to-date,

monitored and governed by their quality policy and objectives. Table 4.4 below presents the methods used to measure effectiveness by each company.

TABLE 4.4 – EFFECTIVENESS MEASUREMENT METHODS

Method	Company 1	Company 2	Company 3	Company 4	Company 5
Action completion on time – setting a deadline based on project complexity	Yes	Yes	Yes	Yes	Yes
CAPA FTT (First Time Through)	No	No Each CAPA is tracked	No	Yes	Yes
Repeat/ Recurrence of Issue (e.g. Paynter Chart)	No	Yes Recurring CAPAs are tracked	Yes	No. Working on reports for this.	Yes
Corrective Action vs. Preventive Action Ratio	No	No	Yes	No Will evaluate as more sites develop preventive action	Yes
Other Methods	N/A	Periodic meetings to review CAPA activities	Require effectiveness checks as follow-ups when the CAPA is completed	On time investigations	Perform effectiveness checks at a delay of CAPA completion. Measure frequency of categories and depts.

Two important questions posed to the company were numbers 16 and 19 on the questionnaire. Question 16 asked, “How does your application affect the following items?” The items were:

- Recurring CAPAs
- Number of CAPAs
- Prevention/ correction efforts of CAPAs
- If possible provide types, numbers of recurring, problematic CAPAs

Recurring CAPAs indicate that the system is not functioning effectively. Each company provided a different answer showing that their interpretation of the regulations and their application is a company-based and even case-based decision. At Company 2, recurring CAPAs are visible at the corporate level and are accorded special attention for more effective resolution and verification. At Company 3, recurring CAPAs are trended (i.e. monitored over time for common tendencies/situations) company wide and they try to ensure that program communication insures action so that recurring situations are not seen. Company 4 has seen an elevation in the status of recurring corrective actions based upon their updated process. Company 1 handles recurring CAPAs on a case by case basis. Company 5 has not seen any recurring CAPAs as yet since their CAPA system is still relatively new.

The part of the questionnaire regarding the number of CAPAs was not clearly understood by each company. The question asked for a current quantitative number of CAPAs existing within each company’s CAPA system. Company 2 does not have limits, and CAPAs are initiated as merited. Company 3 logs and trends all CAPAs. Company 1 has changed their criteria for determining a CAPA and this has reduced the number of CAPAs. Company 4 stated that their updated process reduced the number of incidents classified as corrective action; however it has increased the actual amount of corrections and corrective actions. Company 5 quarterly management review addresses the number of CAPAs and any actions needed to reduce the number.

The prevention/correction efforts of Company 2 are handled by periodic meetings to review status and progress. Company 3 handles this same situation by independent quality review of all CAPAs to ensure appropriate resolutions are implemented. Company 1 has started to shift their focus from corrective actions to preventive actions. Company 4 stated that their updated process has strengthened the efforts to correct and prevent recurrence of situations, and that they are currently working to address the documentation of more preventive actions. Company 5 is attempting to bring their system more under control than in issuing preventive actions.

Company 1 and Company 5 were able to provide examples of problematic/recurring CAPAs. For Company 1 the issues stem from post market complaints, and for Company 5 their problematic CAPAs have stemmed from third party audits and are company wide.

Question 19, asked if the following are performed within the CAPA system:

- Follow up investigation to review effectiveness, by who and the measure of effectiveness
- Tracking and trending of CAPAs
- Management review. Involves what disciplines
- Investigation of root causes

Each company performs all of the items on their CAPA system. Company 2 does not define a specific person or group to perform the effectiveness check. The measure of effectiveness is ‘as defined’ typically to ensure adequate implementation of corrective and preventive actions coupled with an audit of methodology and corresponding metrics. They track and trend CAPAs using monthly reports to management, manufacturing sites, division and corporate levels. Management review is also performed by quarterly meetings that involve disciplines such as: Quality, Regulatory, Marketing, R&D, Operations together forming a cross-functional operation. Company 2 used the DMAIC (Define, Measure, Analyze, Improve, Control) process to investigate root causes.

At Company 3, the original assigner of the investigation is responsible for performing the effectiveness check. The measure of effectiveness is dependent upon the situation. They track and trend their CAPAs and perform management review, which involves the following disciplines: All division Heads – Executive, RA/QA, R&D, Operations, Marketing and Clinical. They also investigate their root causes. Company 4 has either a quality professional or a subject matter expert perform the effectiveness check. The measure of effectiveness changes based on the incident and corrective action performed. It can be a reassessment, trending or a test. They also track and trend their CAPAs which is done on both the local and Global levels. Company 4 does perform management review on both the local and Global levels. Global management review is attended by global senior management. All applicable elements of the quality management system are reviewed and these elements to be reviewed are identified in their Quality Policy. Company 4 also investigates their root causes and identifies them for each corrective or preventive action.

Company 5 has non-involved quality personnel perform their effectiveness checks, and the measure of effectiveness again is specific to the nature of the CAPA. Their CAPA review board determines if an effectiveness check is required and what it will involve. Similarly they also perform tracking and trending of CAPAs, management review and investigation of root causes. Company 1 also has quality professional perform their effectiveness checks. The measure for effectiveness is ensuring that the actions taken were appropriate and effective. Company 1 also performs tracking/ trending of CAPAs, and management review involving: complaints, process performance, changes, quality system, organization barriers, and new regulatory requirements. CAPAs are initiated as needed in management review. Investigation of root causes is also performed on their CAPA system.

As stated previously improvements are part of CAPA, and within medical device companies there is always room for process/product or performance improvements. Table 4.5 below depicts the areas for improvement identified by each company.

TABLE 4.5 – AREAS FOR IMPROVEMENT

Company	Improvement
Company 1	Tracking/ trending. Training/ awareness
Company 2	Training/ awareness. Greater ownership by responsible persons to meet deadlines and provide organized documentation to "tell the story'.
Company 3	Greater efficiency
Company 4	More thorough investigations, training/ awareness, training to improve the depth of investigation and create awareness of the benefits of a complete and thorough investigation
Company 5	Tracking/ trending. Training/ awareness

Quality System Regulation, 21 CFR 820, requires that CAPA information be disseminated to the involved personnel. All of the companies employ this practice. Company 2 has periodic meetings; monthly, quarterly at a minimum and ad-hoc as determined appropriate. Company 3 provides the group managers with the CAPA meeting minutes for distribution to their staff, Standard Operating Procedure (SOP) changes are communicated corporate wide on occurrence. Company 1 disseminated information at Management Review which occurs on a monthly basis. Company 4 provides CAPA information to management on a monthly basis and currently to the CEO on the same timeframe. The information is also included in the management review at least twice a year. Company 5 disseminates their information from their CAPA review board to the CAPA team leader, who is responsible for working with various department heads and subject matter experts to complete the action. The CAPA team leader is also responsible for notifying any affected personnel of any system/process changes that the CAPA requires.

CHAPTER 5

Conclusions

5.1 Summary

The Corrective Action and Preventive Action (CAPA) system is an integral element of the medical device industry process, based on the research and companies evaluated. It acts as a vehicle for the production of safe and effective product that meets predetermined quality characteristics and specifications and ensures that there is a system for continued improvement of product, process and systems.

From the research presented in this assessment, it can be concluded that the two documents governing Quality System Regulation (QSR): FDA regulation, 21 CFR 820-Quality System Regulation and ISO 13485:2003, Medical Devices – Quality Management Systems – Requirements for Regulatory Purposes, both define the requirements for establishing and maintaining procedures for a CAPA system. The FDA document, 21 CFR 820, provides a more detailed outline of how a company should deal with corrective and preventive actions. The FDA regulatory document is law and should be viewed as the primary document for establishing a CAPA system. The significance of the differences is important, and 21 CFR 820 should be viewed as the primary document when developing a CAPA system. 21 CFR 820 includes areas such as statistical methodology, verification/validation of effectiveness, management review and dissemination of information to involved personnel.

Each of these items strengthens a CAPA system and the overall process/system. Statistical methodology application such as Six Sigma and Lean Manufacturing has become increasingly acceptable in medical device companies. Six Sigma and Lean Manufacturing seek to improve quality of process outputs by identifying and eliminating causes of errors in manufacturing processes and systems (Reference #7 and #8). Six Sigma is a business management strategy that utilizes quality management methods, including statistical to improve the quality of process outputs by identifying and removing defects, Six Sigma provides creates a specialized network of people within a company, and certifies the individuals – Green Belt, Black Belt and Master Black Belt – as experts in this area (Reference #7). Lean Manufacturing is a production practice that considers the expenditure of resources for any goal other than the creation of value for the end customer to be wasteful, and thus a target for elimination (Reference #8). Verification/validation of effectiveness is always going to be vital to the CAPA system as it provides documented evidence that the actions implemented are acceptable, work and don't negatively impact other areas of the process or product. This adds an extra step of awareness and confidence in the corrective/preventive action implemented.

Management review is also fundamental to the CAPA system. Ensuring that the corrective/preventive action is acceptable all the way to the management level allows for the action to be in line with company policies and objectives, and it ensures that management is aware of the day-to-day operations and has visible input on the decisions made. Disseminating the information regarding the changes and actions to the involved personnel is also critical as it allows for proper training on the actions, changes and procedures, and creates a sense of accountability and awareness to the corrective/preventive action, the original discrepancy. This is beneficial to a company because employees will be able to identify future nonconformities and will know the process to resolve them. Management review and dissemination of information to those involved are also important in establishing an open line of communication

and information passage. Situations can occur where nonconformities arise and persist due to lack of communication, information not being passed down to the correct personnel or information being passed on a “need to know” basis. This has the potential to hinder the CAPA system because the persons involved directly with the nonconformity are not involved in the investigation, analysis or action plan and are therefore not aware of the corrective/preventive action taken.

5.2 Industry Summary

From the questionnaires, it can be determined that industry utilizes both 21 CFR 820 and ISO 13485:2003 to establish and maintain procedures for their Corrective and Preventive Action systems. Company 5 felt that the FDA Quality System Regulation provided more detail and rules for establishing and maintaining a CAPA system and stated that they would always look to that document first, while the other companies all felt that they implemented the documents equally when developing their CAPA system. Also of interest was the fact that all the companies, except Company 5, who are working on theirs at this time, have their ISO certification for ISO 13485:2003. This shows that all of them place importance on the certification and the international standard and see it as a beneficial advantage to their company. For companies such as Company 2, Company 3, Company 1 and Company 4 who market products globally and have locations outside the US, having an internationally recognized certification shows suppliers, customers, and regulatory bodies that they will go the extra mile to ensure that they are compliant in their processes/ systems, and produce safe and effective product.

All the companies, except Company 3 mentioned training/ awareness as an improvement they would like to see take place in their company’s CAPA system. One aspect of an effective CAPA system is that employees are trained on the procedures and aware of them and the process.

Lack of training and awareness on the procedures can result in employees not being knowledgeable in identifying, investigating, analyzing and resolving a nonconformity, and sometimes these can go undocumented because of inadequate training. All of the companies stated that their CAPA system was effective, perform effectiveness checks and utilize various methods for measuring effectiveness. Therefore, it can be determined that if their CAPA systems are effective, that employees are trained and aware of the CAPA system and procedures. Therefore, training and awareness are present but need to be evaluated for continual improvement.

From the questionnaires, it can also be determined that the FDA regulation, 21 CFR 820 is slightly dominant over ISO 13485:2003. Based on the stated differences between the two regulations, each company has implemented the following into their procedures: management review, verification/validation, and dissemination of information to involved personnel. Each company uses methods such as periodic review/meetings, management review, validated databases, CAPA teams and team leaders, group managers, and CAPA meeting minutes. They all have validated CAPA databases; perform tracking/trending and follow-up investigations to review effectiveness of the action plan.

Each of the five companies provided some response to all 25 questions. Based on the expected answers for the questions, 14 of the 25 questions were 100% completed, 3 of the 25 questions were 80% completed, 4 questions were 60% completed, 2 questions were 40% completed and 1 question was not completed by any of the companies. Eight questions had partial answers from various companies, and no company answered 100% of the questions. Individual expected results for each company were as follows: Company 1 – 72%, Company 2 – 72%, Company 3 – 88%, Company 4 – 84% and Company 5 – 88%.

5.3 Recommendations and The Future

Based on the research and questionnaire responses, it can be determined that the two regulations are effective in providing requirements for establishing and maintaining procedures for a CAPA system. However, CAPA is about continuous improvement in the process/system, therefore there is always room for improvement. Some recommendations for the future are:

- Develop a more in-depth survey with questions that provide more accurate responses.
- Conduct face-to-face interviews with the CAPA personnel at each company, if possible, to gain more accurate information and view first hand the CAPA system and its implementation.
- Implement more quantitative methods to assess the impact of 21 CFR 820 and ISO 13485:2003 on CAPA systems, where feasible, in order to obtain data that can be statistically evaluated.
- Conduct interviews with personnel who are impacted by the CAPA system at companies to determine the effectiveness of the CAPA system and its practice within the company.
- Include a larger variety of medical device companies, varying in manufactured device, location, size, existence in industry

Looking at the two documents, one may ask why these documents are not combined or do not mirror each other more closely. The Global Harmonization Task Force (GHTF) started this undertaking. The GHTF was created in 1992 with the purpose of responding to the rising need for international harmonization in the regulation of medical devices (Reference #11). In 2008 at their annual meeting they began discussions on a working draft for a guidance document on ‘Quality Management System – Medical Devices – Guidance on Corrective and Preventive Action (CAPA) Principles and Activities (Reference #11). The current discussions on this document are that not all discrepancies identified within the quality system require “CAPA”, and some may not even get to that level, but can be resolved exclusively with corrections

(Reference #11). Discussions were also raised concerning the need to include in the data analysis activity a review across various appropriate data sources to ensure actions are taken at all appropriate points (Reference #5). Once these discussions are resolved and more work is done by the GHTF, this document will be at the forefront of the two regulatory documents 21 CFR 820 and ISO 13485:2003 for establishing and maintaining CAPA systems.

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APPENDIX A

Interview Questionnaires

Michelle Whittaker

PHAR 7300 – Masters Thesis

Master of Science in Regulatory Affairs

Thesis Project

Quality System Regulation: ISO 13485 and 21 CFR 820 and their impact on CAPA systems

INTERVIEW QUESTIONS

1. Your name, title, company and location? Company 1

2. What type of medical device does your company manufacture and market?
   a. Class? II and III
   b. Implantable? No
   c. Purpose? Vision Correction

3. How long has your company been in business?
   ☐ 0-5 years ☐ 6-10 years ☐ 11-15 years ☐ 16-20 years ☒ 20 or more years

4. Which of the two regulations are used by your company? Or does your company use both? Both

5. Is your company ISO 13485 certified? Yes. If so, What approach did you use to attain the certification? Procedures were written and a Quality Manual was implemented. Certified by BSi

6. Does your company have procedures in place to implement, maintain CAPAs? Yes

7. Does your company have a documented CAPA system? Yes

8. What is your company's definition of CAPA system?
   Corrective Action = Action to eliminate the causes and reoccurrence of detected nonconformities and other quality related issues.
   Preventive Action = Action to eliminate the potential cause and occurrence of nonconformities and other quality related issues

9. How does your company apply the two documents to your CAPA system? The system is compliant and meets the requirements of CFR 820 and 13485

10. Is your CAPA system oriented to systemic issues or does it include corrective actions for all remediation for deviations? Nonconformities identified in Mgmt Reviews, Product/Validations, Process/Systems, Supplier Performance, Postmarket, Internal/External Auditing, Product Development, Quality System Elements.

11. What criteria is used to open a CAPA? See above

12. Is one regulation followed more than the other? No

13. In your opinion do the two documents provide a similar or different approach to the CAPA system? They provide a similar approach

14. Is your application of these regulations effective? Yes
    a. If yes, why? I feel that there has been a lot of emphasis on improving the effectiveness over the last few years. This needs to continue

    b. If no, what changes would you implement or like to see implemented to improve effectiveness?

15. Do you use methods such as the following to measure the effectiveness?
    a. Action completion on time by setting a date of completion based on the complexity of the project and meeting the deadline. ☒ Y ☐N
    b. CAPA FTT (First time through): measuring how many action reports are rejected back to the appointed team due to incomplete information or insufficient investigation, action, or steps to prevent. ☐Y ☒ N
    c. Repeat or recurrence of issue method, such as a Paynter chart. ☐Y ☒ N
    d. Corrective action vs. Preventive action ratio. ☐Y ☒ N
    e. Other. Please list

16. How does your application affect the following items?
    a. Recurring CAPAs - Recurring CAPAs are handled on a case by case basis.

b. Number of CAPAs - The criteria for CAPAs was changed in 2008. This has reduced the number of CAPAs

c. Prevention/ correction efforts of CAPAs - Corrective Action has always been focused on more than prevention. There is now more focus on prevention

d. If possible can you provide some numbers, types of CAPAs that are recurring, problematic? - 0065, 0122, 0116, 0103, and 0110 are all post market related complaints.

17. Does your company keep documented records of all CAPAs? If yes, how long are these maintained?
    The retention requirement is a minimum of 3 years, however they are kept longer.

18. Does your company have a validated tracking database for your CAPA system? Yes

19. Does your company perform the following on your CAPA system
    a. Follow up investigations to review effectiveness. Yes
        i. Who performs effectiveness check? Quality

        ii. What is the measure for effectiveness? To ensure the actions taken were effective

    b. Tracking and trending of CAPAs Yes

    c. Management review Yes
        i. Involves what disciplines?
        The following is reviewed in Mgmt Review – Complaints, Process Performance, Changes, Quality System, Organization Barriers and New regulatory requirements. CAPAs are initiated as needed in Mgmt Review

    d. Investigation of root causes Yes

20. Are the items listed below governed by company procedures?
    a. Follow up investigations to review effectiveness- Yes
    b. Tracking and trending of CAPAs- Yes
    c. Management review- Yes
    d. Investigation of root causes- Yes

21. What improvements would you like to see take place in your company's CAPA system?
    a. ☒X tracking/ trending
    b. ☐ more thorough investigations
    c. ☐ effectiveness checks
    d. ☐ management involvement
    e. ☒X training / awareness
    f. ☐ Other. Please list

    _____

    _____

22. What areas in your opinion are lacking in the regulation that you think should be introduced to make it more effective? None

23. As practice how is your CAPA information communicated to the appropriate personnel to inform them of the issues arising in the company? What mechanism and frequency are utilized? Mgmt Review at a minimum of 2x per year.

24. What other information regarding ISO 13485 21 CFR 820 and their approach to CAPA systems would you like to include? None

25. Are there other key areas of the two regulations that you find compare or contrast their approach to the manufacture and maintenance of medical devices No

Thank you for taking the time to complete this assessment. I am going to use this survey to support my Masters Thesis research. Your cooperation was greatly appreciated.

Please note than any/all company information collected for this thesis will be confidential and will not be shared or used for any other purpose.

Thank you

Michelle A. Whittaker

Michelle Whittaker

PHAR 7300 – Masters Thesis

Master of Science in Regulatory Affairs

Thesis Project

Quality System Regulation: ISO 13485 and 21 CFR 820 and their impact on CAPA systems

INTERVIEW QUESTIONS

1. Your name, title, company and location? Company 3

2. What type of medical device does your company manufacture and market?
   a. Class? III
   b. Implantable? Yes
   c. Purpose? Use as an adjunct to sutures and staples at vascular anastomoses. Also replacement decellularized heart valve as a second device.

3. How long has your company been in business?
   ☐ 0-5 years ☐ 6-10 years ☐ 11-15 years ☐ 16-20 years ☒ 20 or more years

4. Which of the two regulations are used by your company? Or does your company use both? 13485 and 820. Both.

5. Is your company ISO 13485 certified? If so, What approach did you use to attain the certification? We performed a gap analysis between our existing Quality System and what was called for in the ISO 13485:2003 Quality System Standard and put in place measures to address any gaps.

6. Does your company have procedures in place to implement, maintain CAPAs? Yes.

7. Does your company have a documented CAPA system? Yes.

8. What is your company's definition of CAPA system? The program by which we investigate, document, and trend Corrective and Preventive Actions.

9. How does your company apply the two documents to your CAPA system? Our SOP on CAPA was generated to address all aspects required for both the QSR as well as ISO 13485:2003. Each year the program is audited to insure it is staying on track.

10. Is your CAPA system oriented to systemic issues or does it include corrective actions for all remediation for deviations? Focus is on systemic issues, but where an isolated instance is deemed a critical failure (ex. Final product, packaging) it is incorporated into the CAPA program. I would suggest that 75 to 85% of remediations for deviations are addressed in the CAPA program.

11. What criteria is used to open a CAPA? The recognition to take an action to either correct or prevent a situation which could result in a product or process deviation.

12. Is one regulation followed more than the other? No

13. In your opinion do the two documents provide a similar or different approach to the CAPA system? Similar documents, but in practice our notified body has focused much more on preventive actions and effectiveness checks than FDA investigators have to date.

14. Is your application of these regulations effective? Yes
    a. If yes, why? It needs to be if we are to maintain our product approvals and Quality System certification. The actions we take frequently address the root of the problem at hand and prevent it from recurring in that form.

    b. If no, what changes would you implement or like to see implemented to improve effectiveness?
15. Do you use methods such as the following to measure the effectiveness? We require Effectiveness Checks as follow-ups after the CAPA has been completed.
    a. Action completion on time by setting a date of completion based on the complexity of the project and meeting the deadline. ☒Y ☐N
    b. CAPA FTT (First time through): measuring how many action reports are rejected back to the appointed team due to incomplete information or insufficient investigation, action, or steps to prevent. ☐Y ☒N, not directly
    c. Repeat or recurrence of issue method, such as a Paynter chart. ☒Y ☐N
    d. Corrective action vs. Preventive action ratio. ☒Y ☐N
    e. Other. Please list

16. How does your application affect the following items?
    a. Recurring CAPAs – we trend for this across the company and try to insure that program communication can insure thorough action address such that we do not see recurring situations.

b. Number of CAPAs – Affect this? We log and trend all CAPAs

c. Prevention/ correction efforts of CAPAs – the independent Quality function reviews all CAPAs to insure resolutions are appropriate for the issue at hand.

d. If possible can you provide some numbers, types of CAPAs that are recurring, problematic? N/A

17. Does your company keep documented records of all CAPAs? If yes, how long are these maintained? Yes, forever. They are archived and never destroyed.

18. Does your company have a validated tracking database for your CAPA system? Yes

19. Does your company perform the following on your CAPA system
    a. Follow up investigations to review effectiveness Yes
        i. Who performs effectiveness check? Original assigner of the investigation

        ii. What is the measure for effectiveness? Depends on the issue at hand.

    b. Tracking and trending of CAPAs: Yes
    c. Management review Yes
        iii. Involves what disciplines? Heads of all of the divisions of the company – Executive, RA/QA, Operations, Marketing, Clinical, R&D.

    d. Investigation of root causes Yes

20. Are the items listed below governed by company procedures?
    b. Follow up investigations to review effectiveness Yes
    c. Tracking and trending of CAPAs Yes
    d. Management review Yes
    e. Investigation of root causes Yes

21. What improvements would you like to see take place in your company's CAPA system?
    b. ☐ tracking/ trending
    c. ☐ more thorough investigations
    d. ☐ effectiveness checks
    e. ☐ management involvement
    f. ☐ training / awareness
    g. ☒ Other. Please list Greater efficiency

22. What areas in your opinion are lacking in the regulation that you think should be introduced to make it more effective? None

23. As practice how is your CAPA information communicated to the appropriate personnel to inform them of the issues arising in the company? What mechanism and frequency are utilized? CAPA Meeting minutes to group managers, with communicate to their staff. SOP changes are distributed corporate wide.

24. What other information regarding ISO 13485 21 CFR 820 and their approach to CAPA systems would you like to include? None

25. Are there other key areas of the two regulations that you find compare or contrast their approach to the manufacture and maintenance of medical devices None

Thank you for taking the time to complete this assessment. I am going to use this survey to support my Masters Thesis research. Your cooperation was greatly appreciated.

Please note than any/all company information collected for this thesis will be confidential and will not be shared or used for any other purpose.

Thank you

Michelle A. Whittaker

Michelle Whittaker

PHAR 7300 – Masters Thesis

Master of Science in Regulatory Affairs

Thesis Project

Quality System Regulation: ISO 13485 and 21 CFR 820 and their impact on CAPA systems

INTERVIEW QUESTIONS

1. Your name, title, company and location? Company 5

2. What type of medical device does your company manufacture and market?
   a. Class? II
   b. Implantable? No
   c. Purpose? Cell delivery system

3. How long has your company been in business?
   ☐ 0-5 years ☒ 6-10 years ☐ 11-15 years ☐ 16-20 years ☐ 20 or more years

4. Which of the two regulations are used by your company? Or does your company use both? Both

5. Is your company ISO 13485 certified? If so, What approach did you use to attain the certification? We have not obtained certification – we have auditors coming in at the beginning of next year to obtain certification.

6. Does your company have procedures in place to implement, maintain CAPAs? Yes.

7. Does your company have a documented CAPA system? Yes.

8. What is your company's definition of CAPA system? The CAPA system is in place to prevent the onset or recurrence of nonconformities, defects, or other undesirable situations.

9. How does your company apply the two documents to your CAPA system? Both regulations specify certain pieces of a CAPA system that needs to be in place. 21 CFR 820 gives more specific details, but all required components of the CAPA system per both regulations are carried over to our CAPA system.

10. Is your CAPA system oriented to systemic issues or does it include corrective actions for all remediation for deviations? Systemic issues. We use nonconformance reports to cover specific deviations.

11. What criteria is used to open a CAPA? A CAPA can be opened through any of the following – component/product failure, process/procedure failure, overdue calibration/ equipment failure, internal compliance audit, supplier audit, third party inspection, field report investigation/complaint (and of course there's an other category)

12. Is one regulation followed more than the other? 21 CFR 820 has more specific details in terms of what is required – ISO 13485 is very broad and general. I would say our specifics come more from 21 CFR 820**.**

13. In your opinion do the two documents provide a similar or different approach to the CAPA system? Similar, but again, 21 CFR 820 provides more specific details.

14. Is your application of these regulations effective?
    a. If yes, why? Currently no, but we are in the process of revamping the system to bring it more under control.
    b. If no, what changes would you implement or like to see implemented to improve effectiveness? There needs to be more accountability of assigned parties and a more effective system of tracking open CAPAs, length of time open, actions taken to date, etc.

15. Do you use methods such as the following to measure the effectiveness?
    a. Action completion on time by setting a date of completion based on the complexity of the project and meeting the deadline. ☒Y ☐N
    b. CAPA FTT (First time through): measuring how many action reports are rejected back to the appointed team due to incomplete information or insufficient investigation, action, or steps to prevent. ☒Y ☐N
    c. Repeat or recurrence of issue method, such as a Paynter chart. ☒Y ☐N
    d. Corrective action vs. Preventive action ratio. ☒Y ☐N
    e. Other. Please list. We also perform effectiveness checks at a delay from CAPA completion to verify that the action was acceptable. We measure frequency of categories and depts. Involved as well.

16. How does your application affect the following items?
    a. Recurring CAPAs- It hasn't been an issue to date – our CAPA program is relatively new. We will measure this but there hasn't been any issues so far.

b. Number of CAPAs- Quarterly management review addresses the number of CAPAs (as well as any recurring if/when that becomes a problem and category, etc.) and any actions needed to bring the number down.

c. Prevention/ correction efforts of CAPAs. To date our CAPA system has been more involved in bringing things under control than in issuing preventive actions. Once we have a handle on our current problem areas we'll start focusing more on improving things.

d. If possible can you provide some numbers, types of CAPAs that are recurring, problematic? Most of our CAPAs came from one third party audit and they're spread out over the whole company so I can't really give you any meaningful information for this.

17. Does your company keep documented records of all CAPAs? If yes, how long are these maintained? Yes, and indefinitely.

18. Does your company have a validated tracking database for your CAPA system? Unfortunately, no, but we're hoping to soon.

19. Does your company perform the following on your CAPA system
    a. Follow up investigations to review effectiveness
        i. Who performs effectiveness check? Non-involved Quality personnel.

        ii. What is the measure for effectiveness?
            It really depends on the specific nature of the CAPA as to what the best means of measuring the effectiveness is. Our CAPA review board determines if a check is needed and what it will involve.

    b. Tracking and trending of CAPAs Yes.

    c. Management review Yes.
        i. Involves what disciplines? I'm not sure what you mean here.

    d. Investigation of root causes Yes.

20. Are the items listed below governed by company procedures?
    a. Follow up investigations to review effectiveness. Yes, in that they are required. There aren't any details of how to do the check.
    b. Tracking and trending of CAPAs Yes.
    c. Management review Yes.
    d. Investigation of root causes Yes.

21. What improvements would you like to see take place in your company's CAPA system?
    a. ☒ tracking/ trending
    b. ☐ more thorough investigations
    c. ☐ effectiveness checks
    d. ☐ management involvement
    e. ☒ training / awareness
    f. ☐ Other. Please list _____

22. What areas in your opinion are lacking in the regulation that you think should be introduced to make it more effective? 21 CFR is a pretty good regulation, I think – it provides a good level of detail as to what needs to be involved without being constricting. ISO, on the other hand, is very broad in terms and not very helpful in determining what needs to be in place for a CAPA program.

23. As practice how is your CAPA information communicated to the appropriate personnel to inform them of the issues arising in the company? What mechanism and frequency are utilized? Information disseminates from the CAPA review board to the CAPA team leader, who is responsible for working with various department heads or subject experts to complete the action. This individual is also responsible for notifying appropriate personnel about any system or process changes that the CAPA requires.

24. What other information regarding ISO 13485 21 CFR 820 and their approach to CAPA systems would you like to include? I think I've pretty well covered it.

25. Are there other key areas of the two regulations that you find compare or contrast their approach to the manufacture and maintenance of medical devices I think my comments on ISO vs. CFR apply pretty much throughout the regulations. CFR is a much more specific regulation, giving more guidance and support in developing systems in general, while ISO is very nonspecific. In terms of the usefulness of one versus the other, I would almost always look to CFR before ISO.

Thank you for taking the time to complete this assessment. I am going to use this survey to support my Masters Thesis research. Your cooperation was greatly appreciated.

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Thank you

Michelle A. Whittaker

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PHAR 7300 – Masters Thesis

Master of Science in Regulatory Affairs

Thesis Project

Quality System Regulation: ISO 13485 and 21 CFR 820 and their impact on CAPA systems

INTERVIEW QUESTIONS

1. Your name, title, company and location? Company 2

2. What type of medical device does your company manufacture and market?
   a. Class? 1 and 2.
   b. Implantable? A few; women's continence, urethral stents
   c. Purpose? Gastroenterology

3. How long has your company been in business?
   ☐ 0-5 years ☐ 6-10 years ☐ 11-15 years ☐ 16-20 years ☒ 20 or more years

4. Which of the two regulations are used by your company? Or does your company use both? Both

5. Is your company ISO 13485 certified? If so, What approach did you use to attain the certification? Yes. Don't know, was not here; not clear on meaning of 'approach'. Surveillance audits continue on an annual basis with recertification every three years.

6. Does your company have procedures in place to implement, maintain CAPAs? Yes.

7. Does your company have a documented CAPA system? Yes.

8. What is your company's definition of CAPA system? The CAPA system is defined by the requirements of the standards noted above.

9. How does your company apply the two documents to your CAPA system? They define the compliance requirements for the CAPA system.

10. Is your CAPA system oriented to systemic issues or does it include corrective actions for all remediation for deviations? It is primarily focused on systemic issues, but also incorporates issues judged by management to be critical.

11. What criteria is used to open a CAPA? CAPAs are initiated after completing a CAPA Determination Form or a Preliminary Assessment.

12. Is one regulation followed more than the other? Both are followed about equally.

13. In your opinion do the two documents provide a similar or different approach to the CAPA system? Similar. Compliance with one meets much of the other.

14. Is your application of these regulations effective? Yes.
    a. If yes, why? The CAPA system has proven to be a systemic methodology to identify root causes, corrective and preventive actions, and verify effectiveness.

    b. If no, what changes would you implement or like to see implemented to improve effectiveness?

15. Do you use methods such as the following to measure the effectiveness?
    a. Action completion on time by setting a date of completion based on the complexity of the project and meeting the deadline. ☒Y ☐N
    b. CAPA FTT (First time through): measuring how many action reports are rejected back to the appointed team due to incomplete information or insufficient investigation, action, or steps to prevent. ☐Y ☒N Each CAPA is tracked, but this is not a metric used.
    c. Repeat or recurrence of issue method, such as a Paynter chart. ☒Y ☐N Recurring CAPAs are tracked, but Paynter Chart is not.
    d. Corrective action vs. Preventive action ratio. ☐Y ☒N
    e. Other. Please list Periodic meetings to review CAPA activities.

16. How does your application affect the following items?
    a. Recurring CAPAs - These have visibility to the Corporate level and are accorded special attention for more effective resolution and verification.

    b. Number of CAPAs - Not clear on this question. There are no limits. CAPAs are initiated as merited.

c. Prevention/ correction efforts of CAPAs - Periodic meetings to review status and progress.

d. If possible can you provide some numbers, types of CAPAs that are recurring, problematic? N/A

17. Does your company keep documented records of all CAPAs? If yes, how long are these maintained? Yes. At least 7 years.

18. Does your company have a validated tracking database for your CAPA system? Yes.

19. Does your company perform the following on your CAPA system
    a. Follow up investigations to review effectiveness Yes.
        i. Who performs effectiveness check? As defined – typically with independence from implementation.
        ii. What is the measure for effectiveness? As defined – typically ensuring adequate implementation of corrective and preventive actions coupled with an audit of methodology and corresponding metrics.

    b. Tracking and trending of CAPAs Monthly reports to management; Mfg Sites, Division, and Corporate levels.

    c. Management review Quarterly meetings.
        i. Involves what disciplines? Quality, Regulatory, Marketing, R&D, Operations – comprehensively cross-functional.

    d. Investigation of root causes DMAIC process employed.

20. Are the items listed below governed by company procedures?
    a. Follow up investigations to review effectiveness Yes.
    b. Tracking and trending of CAPAs Yes.
    c. Management review Yes.
    d. Investigation of root causes Yes.

21. What improvements would you like to see take place in your company's CAPA system?
    a. ☐ tracking/ trending
    b. ☐ more thorough investigations
    c. ☐ effectiveness checks
    d. ☐ management involvement
    e. ☒ training / awareness
    f. ☒ Other. Please list

Greater ownership by those responsible to meet due dates and provide organized documentation to 'tell the story'.

22. What areas in your opinion are lacking in the regulation that you think should be introduced to make it more effective? No comment.

23. As practice how is your CAPA information communicated to the appropriate personnel to inform them of the issues arising in the company? What mechanism and frequency are utilized? Periodic meetings; monthly, quarterly at a minimum, and ad-hoc as determined appropriate.

24. What other information regarding ISO 13485 21 CFR 820 and their approach to CAPA systems would you like to include? No comment.

25. Are there other key areas of the two regulations that you find compare or contrast their approach to the manufacture and maintenance of medical devices No comment.

Thank you for taking the time to complete this assessment. I am going to use this survey to support my Masters Thesis research. Your cooperation was greatly appreciated.

Please note than any/all company information collected for this thesis will be confidential and will not be shared or used for any other purpose.

Thank you

Michelle A. Whittaker

Michelle Whittaker

PHAR 7300 – Masters Thesis

Master of Science in Regulatory Affairs

Thesis Project

Quality System Regulation: ISO 13485 and 21 CFR 820 and their impact on CAPA systems

INTERVIEW QUESTIONS

1. Your name, title, company and location? Company 4

2. What type of medical device does your company manufacture and market?
   a. Class? 2 & 3
   b. Implantable? No
   c. Purpose? For the correction of vision and the promotion of healthy eyes

3. How long has your company been in business?
   ☐ 0-5 years ☐ 6-10 years ☐ 11-15 years ☐ 16-20 years ☒ 20 or more years

4. Which of the two regulations are used by your company? Or does your company use both?
   CIBA VISION (CV) uses both regulations in addition the quality module of our parent company Novartis. There is also a ISO guidance document for 13485.

5. Is your company ISO 13485 certified? If so, What approach did you use to attain the certification?
   CV is ISO 13485 certified. CV was first certified ISO 9001:1994 and then EN46001 April 1996. CV obtained approval to apply CE marking to its product in July 1997, a requirement to market in Europe under the MMD (Medical Device Directive) The medical device requirements were moved to ISO 13485 with the creation of the standard in 1996. CV adopted ISO 13485:1996 in December 2002 and now holds certification to the ISO 13485:2003 version of the standard.

6. Does your company have procedures in place to implement, maintain CAPAs? Yes, CV has both procedures and policies for corrective and preventive action and quality document maintenance and retention.

7. Does your company have a documented CAPA system? Yes and validated electronic systems for the documentation and tracking of corrective and preventive action.

8. What is your company's definition of CAPA system? A CAPA system is the set of procedures and processes required to implement and execute the requirements of the CAPA regulations.

9. How does your company apply the two documents to your CAPA system? The requirements of these two documents were evaluated as the system was developed in addition to internal requirements when the procedure and policies were written. The system is evaluated by external auditor to determine compliance to these regulations.

10. Is your CAPA system oriented to systemic issues or does it include corrective actions for all remediation for deviations? Our CAPA system includes all corrective actions. When the system was redesigned, last year the team applied a risk based approach to the handling of non-conformances and deviations requiring corrective or preventive actions.

11. What criteria is used to open a CAPA? The documents that we refer to as CAPA are the highest risk occurrences for CV. There are specific criteria defined in our procedure. However, corrective action can and is applied at the other levels as well. Preventive actions can be only documented when a fix has been made for a potential issue. If the problem has occurred, the occurrence is a corrective action based on the definition from ISO.

12. Is one regulation followed more than the other? No. There are more corrective action than preventive actions.

13. In your opinion do the two documents provide a similar or different approach to the CAPA system? The FDA regulation (21 CFR 820) is based on the previous version of ISO. The approach is similar for medical devices; however the terms are used differently for pharmaceuticals.

14. Is your application of these regulations effective?
    a. If yes, why? Yes, our recent inspections have not resulted in finding against the system.

    b. If no, what changes would you implement or like to see implemented to improve effectiveness? N/A, we expect to be doing some tweaking of the system later this year to provide a smoother functionality for the users.

15. Do you use methods such as the following to measure the effectiveness?
    a. Action completion on time by setting a date of completion based on the complexity of the project and meeting the deadline. ☒Y ☐N
    b. CAPA FTT (First time through): measuring how many action reports are rejected back to the appointed team due to incomplete information or insufficient investigation, action, or steps to prevent. ☒Y ☐N
    c. Repeat or recurrence of issue method, such as a Paynter chart. ☐Y ☒N We are working on reports to provide this data
    d. Corrective action vs. Preventive action ratio. ☐Y ☒N we will evaluate as more sites create preventive actions.
    e. Other. Please list On time investigations

16. How does your application affect the following items?
    a. Recurring CAPAs –The updated process elevated the status of recurring CA
    b. Number of CAPAs – The update process reduced the number of incidents classified as CA however it has increased the amount of corrective actions and corrections.

    c. Prevention/ correction efforts of CAPAs – The updated process has strengthened the efforts to correct and prevent recurrence of situations. We are now working to address the documentation of more preventive actions

    d. If possible can you provide some numbers, types of CAPAs that are recurring, problematic? This data is internal use only.

17. Does your company keep documented records of all CAPAs? If yes, how long are these maintained? Yes, CV keeps CAPA data for the time period required by our record retention policy.

18. Does your company have a validated tracking database for your CAPA system? Yes, we have three validated systems. Two are Lotus Notes based and will be retired before the end of the year and the other is a TrackWise system.

19. Does your company perform the following on your CAPA system
    a. Follow up investigations to review effectiveness – We perform effectiveness checks but they are not necessary an investigation
        i. Who performs effectiveness check? Either a quality professional or an subject matter expert.

        ii. What is the measure for effectiveness? The measure of effectiveness changes based on the incident and corrective action preformed. It can be a reassessment, trending or a test.

b. Tracking and trending of CAPAs – yes, this is done local at the sites and Global by my department

c. Management review– yes, this is done local at the sites and Global by my department
    i. Involves what disciplines? The Global Management review is attended by the senior management of CV globally. All applicable elements of the quality management system are reviewed. The elements to be reviewed are identified in our Quality Policy for management review.

d. Investigation of root causes- The investigation and identification of a root cause is required for each corrective or preventive action.

20. Are the items listed below governed by company procedures?
    a. Follow up investigations to review effectiveness Yes
    b. Tracking and trending of CAPAs Yes
    c. Management review Yes
    d. Investigation of root causes Yes

21. What improvements would you like to see take place in your company's CAPA system?
    a. ☐ tracking/ trending
    b. ☒ more thorough investigations
    c. ☐ effectiveness checks
    d. ☐ management involvement
    e. ☒ training / awareness
    f. ☒ Other. Please list I think now that we have a complaint system in place that training is need to improve the depth of investigation and make people aware of the benefits of a complete and thorough investigation.

22. What areas in your opinion are lacking in the regulation that you think should be introduced to make it more effective? I think the regulation is good, I like the revision done in the ISO 9000:2008 where the word correction was added making it clear that a company can not eliminate all incidents and sometimes will only correct a situation instead of suggesting that a company can do a corrective action in all incidents where the situation is never seen again. This change is expected to be adopted in the next version of ISO 13485.

23. As practice how is your CAPA information communicated to the appropriate personnel to inform them of the issues arising in the company? What mechanism and frequency are utilized? The CAPA information is provided to my management on a monthly basis and currently our CEO is receiving it monthly as well. The information is also included in the management review and is provided in that format at least twice a year.

24. What other information regarding ISO 13485 21 CFR 820 and their approach to CAPA systems would you like to include? N/A

25. Are there other key areas of the two regulations that you find compare or contrast their approach to the manufacture and maintenance of medical devices? The FDA is compliance driven versus ISO that is systems driven.

Thank you for taking the time to complete this assessment. I am going to use this survey to support my Masters Thesis research. Your cooperation was greatly appreciated.

Please note than any/all company information collected for this thesis will be confidential and will not be shared or used for any other purpose.

Thank you

Michelle A. Whittaker