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FDA Warning Letters, Consequences and Costs to the US Medical Device Industry

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Abstract

To launch or keep a medical device on the US market, FDA pre-approval or continued approval is required. After product approval, the FDA routinely conducts surveillance inspections of medical device companies. The present study looks at issues related to medical device CAPA and the associated costs of remediation for non-compliance with the FDA. This study delves into the costs and issues related to medical device companies for failing to meet FDA expectations. The study will examine the issues that the FDA has with medical device CAPA and suggestions on how to remedy them. This information served as the basis for identifying and examining methods to help reduce or eliminate FDA CAPA-related findings for medical device companies to reduce failure related costs and improving the understanding of CAPA requirements and process efficiencies to help reduce the risk of an FDA finding.

Noncompliance with FDA regulations and failure of medical device quality have resulted in substantial additional costs to a medical device company. Non-routine quality events such as major FDA observations, recalls, warning letters, and consent decrees, along with associated warranties and lawsuits cost the industry between $7.5 billion and $9 billion per year on average. Plus, another $1 billion to $2 billion in lost sales of new and existing products.

Keywords: Corrective and preventive actions • Code of federal regulations • Food and drug administration • Quality system inspection technique • Warning letter

Introduction

In the medical device industry in the United States, implementing an effective Corrective And Preventive Action (CAPA) is not only a regulatory requirement, but an essential part of a Quality Management System (QMS). To allow for continuous improvements to achieve superior quality products. The United States Code of Federal Regulations (CFR) outlines the specific legal framework for enforcement and compliance actions by the United States Food and Drug Administration (FDA).

Medical devices are instruments, machines, implants, or other similar articles intended for use in the diagnosis, treatment, or prevention of diseases or other medical conditions. They are designed to support healthcare providers in their efforts to deliver high-quality medical care to patients. Medical devices have a wide range of applications and can be used in various healthcare settings, including hospitals, clinics, and home care [1].

The United States is the largest medical device market in the world. In 2017 the estimated market value of this industry was $156 billion US Dollars. The United States market accounted for over 40% of the medical device market worldwide in 2017. Globally the sales of medical devices were estimated at $380 billion in 2016 [1].

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According to Berkshire- Hathaway the global medical devices market attained a value of USD 562.6 billion in 2022 [2]. The market is further expected to grow to an estimated USD 965.2 billion by 2031. US exports of medical devices has been estimated at $43 Billion US Dollars in 2018 alone according to the United States Department of Commerce. This industry includes almost 2 million direct or indirect jobs. More than 80% of the medical device companies in the United States consist of fewer than 50 employees. [1]

The United States Food & Drug Administration (FDA) has the primary responsibility for regulatory oversight of the medical device industry in the United States and through medical device products imported into the US market. The FDA also issues Warning Letters to a medical device company upon observing violations during an inspection. Before issuing a Warning Letter the FDA requests the medical device company to respond to the deficiencies that are listed in the FDA Warning Letter. If the FDA observes that these responses are unsatisfactory and violations are of regulatory importance and may impact the safety and quality of the product, an official notification of the deficiency in the form of a Warning Letter is issued to the medical device company [3].

The FDA requires the medical device company to have an effective CAPA subsystem to collect information, analyze information, identify, and investigate product and quality problems, and take corrective or preventive actions to prevent their recurrence. Verifying or validating corrective and preventive actions, communicating corrective actions activities to responsible personnel, providing relevant information for management review, and documenting these activities are essential in dealing effectively with product and quality problems, preventing their recurrence, and preventing or minimizing device failures are all expectations of the FDA [3].

The FDA states the most important quality system element is the Corrective And Preventive Action (CAPA) subsystem. Between 2013 and 2019 approximately 50% of medical device firms inspected by the FDA received at least one FDA finding related to a CAPA issue [4]. In fact, almost every year the number one reason medical device companies receive an FDA Form 483 or Warning Letter is because of CAPA-related issues.

The cost of this oversight by the industry has a significant economic

impact on the medical device industry, and ultimately the consumer who may need a medical device. The McKinsey Center for Government estimates that each year FDA Form 483 and warning letters and consent decrees along with associated warranties and lawsuits cost the industry between $2.5 billion and $5 billion US dollars on average. Another $1 billion to $ 2 billion is lost in sales of new and existing products [5].

Regulatory oversight of the medical device industry in the United States

The FDA has the primary role in regulatory oversight over the medical device industry. The FDA can track its roots back to the Pure Food and Drug Act of 1906. It established the precursor to the FDA. This legislation for the first time established a federal agency with oversight of food and drugs [6].

The Pure Food and Drug Act did not address or cover medical devices. In 1938 the Federal Food, Drug and Cosmetic Act (FD &C Act) added medical devices to FDA jurisdiction. The legislation did not require any premarket approvals or regulatory review process. Instead, the law only required that medical device manufacturers place the name and address of the manufacturer or distributor on the name and address of the manufacturer or distributor on the package. Over the next 40 years numerous efforts were made to further expand FDA authority to medical devices. In the interceding years, numerous high-profile events involving public health issues related to medical devices brought the issue of lack of FDA jurisdiction to both the public and legislative community [6].

A medical device is defined within the Food Drug & Cosmetic Act as "... an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is: recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them, intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes" [7].

In 1976 the Medical Device Amendments of 1976 was signed into law. This piece of legislation gave the FDA regulatory authority of all medical devices sold in the US market. The medical device laws have been modified numerous times over the years, but the fundamental effect of this legislation still guides today how the FDA regulates medical devices. All current guidance and thought about how the FDA regulates medical devices has its origins in this legislation [6].

The United States Code of Federal Regulations (CFR) outlines the specific legal framework for enforcement and compliance actions by the FDA. Specifically, the regulations for CAPA requirements are found under 21 CFR 820.100. This regulation outlines the specific processes that a medical device firm must comply with [8].

Medical Device Amendments of 1976 (MDA)

Prior to 1976 the medical device regulations were vague and did not specifically address medical devices. Regulations were directed specifically to food, drugs, and cosmetics.

The Medical Device Amendments of 1976 (MDA) brought in the use of general controls that applied to all medical devices. It requires that all medical device manufacturers adhere to Good Manufacturing Practices (GMP) and requires that the name and address of the manufacturer be readily identifiable to the end-user. The MDA also mandates “adequate directions for use” and safety warning on all medical devices that advises on the safe use of the devices and identify any acts that might render the devise unsafe [9].

Under the of the conditions of the MDA, the FDA is required to register all medical devices and, keep mandatory listing of all medical devices currently being in the US market. The MDA also requires the FDA be notified of any new medical device 90 days before introduction to the public [9].

It authorized the FDA to inspect factories or any facility that manufactures medical devices and permits for the inspection of the relevant records. The MDA authorizes the FDA to direct a manufacturer to repair or replace defective devices. The FDA also require manufacturers to maintain and submit reports of adverse medical events associated with medical devices to the FDA [9].

The quality system inspection technique

In August 1999 the FDA in response to industry and US Congressional input helped create the Quality System Inspection Technique (QSIT) a Guide to Inspection of Quality Systems.

The QSIT provides instructions to FDA Investigators conducting medical device quality systems inspections. It is used in conjunction with the FDA Compliance Program entitled “Inspection of Medical Device Manufacturers (7382.845) (FDA 2015) It provides guidance for FDA inspection of medical device manufacturers against the Quality System Regulation (21 CFR Part 820) and related regulations. This manual is a publicly available resource that industry and interested individuals can reference on how and what FDA Investigators will look at during a QSIT inspection [10].

The process for performing subsystem inspection is based on a “top-down” approach to inspecting. The subsystem approach is designed to help the FDA Investigator determine the firm’s state of compliance in an organized manner [10].

The “top-down” approach begins each subsystem review with an evaluation of whether the firm has addressed the basic requirements in that subsystem by defining and documenting appropriate procedures. This is followed by an analysis of whether the firm has implemented the requirement of that subsystem.

The inspectional objectives of the QSIT are to determine compliance with FDA regulations. The FDA considers CAPA as one of the most important quality systems elements for inspection. Most of an Investigator’s time is spent during the inspection on this single process [10]

FDA Quality Systems regulations are designed with the principle of continuous improvement. Fundamental to this is the CAPA system. The use of corrective and preventive actions must include all elements of the quality system including employee training, procedures, work instructions, development activities, manufacturing products, processes, acceptance and rejection procedures, and distribution and post-sales support [11].

CAPA must clearly outline what actions were taken to identify and correct nonconforming products. The firm must have a CAPA referral process and have a unit or department within the firm to review and analyze all CAPA that the firm generates, CAPA require a written process that outlines all the steps and methods used to do analysis, investigation, and correction of issues. They firm must include a plan of preventive action to avoid the reoccurrence of the same issue(s) [11].

Overview of the medical device Quality Management System (QMS)

The medical device Quality Management System (QMS) is a structured system of procedures covering all aspects of the design, manufacturing, and risk management. The QMS depends on several subsystems for an overall effective QMS. Each of these seven subsystems covers a key element of the overall QMS system. The CAPA system is the most critical of these systems since it focuses on the elimination of nonconformities, QMS Improvements, and a process to verify the effectiveness of the whole QMS [10].

The FDA states the most important quality system element is the corrective and preventive subsystem [10]. While it is important to develop a QMS that meets regulatory requirements and minimizes the risk of findings on an FDA inspection, it is equally as important that the medical device manufacturers can identify and resolve issues with their QMS. The CAPA process is one which will allow the manufacturer to detect issues that have occurred, might resurface, or eliminate a future or current problem.

The FDA inspection focuses on the four main subsystems CAPA, Design Controls, Management Controls, and Production and Process Controls [10].

Corrective and Preventive Actions (CAPA)

Corrective And Preventive Actions (CAPA) are actions that are processes for identifying, documenting, and addressing defects, deficiencies, and nonconformities. Many believe that the CAPA is the immune system of your organization [10].

CAPA is the abbreviation for corrective action and preventive action. Corrective Action refers to the elimination of the cause of an existing nonconformity or undesirable situation to prevent reoccurrence. Preventive Action is the identification and elimination of the cause(s) of potential nonconformities to prevent occurrence. Corrective Action is reactive while Preventive action is proactive in nature. The FDA requires that all issues involving the use of either a corrective or preventive action be documented [10].

When a medical device manufacturer finds an issue there are three types of actions that the firm may take. Corrective or Immediate Action: This eliminates the immediate problem. It doesn't eliminate the issue permanently but allows a process or work to continue.

Corrective Action eliminates the cause of the nonconformity and prevents repetition. Corrective Actions move products, procedures, processes, and projects back to baselines.

Preventive action prevents potential occurrences. This process is used to identify problems before they occur and become bigger problems. This process could be simple, such as routine maintenance on machinery to avoid costly repairs later.

During the inspection process, the FDA Inspector will follow the QSIT guide and answer each of these questions. If the information is lacking the Investigator will note what is missing in each incident and document items that appear to be incorrectly done [12].

FDA warning letters

FDA Warning Letters are notifications issued to medical device companies found to be in significant violation of federal law. Warning Letters represent serious regulatory violations and require prompt corrective action from the recipient [13].

FDA Warning Letters include a detailed explanation of the specific violation and require an immediate response from the manufacturer explaining the corrective action that will be taken. It is important to note that Warning Letters are only issued for violations of regulatory significance meaning that they may lead to enforcement action if corrective actions are not taken [8,13].

For a medical device, FDA Warning Letters can delay or prevent pre-market approval of medical devices. In addition, Warning Letters are published on the FDA website to protect patients and encourage medical device companies to take prompt action. The FDA Warning Letter has several potential legal ramifications such as: the FDA can use it to take regulatory action on the manufacturer, it may be introduced as evidence in a product liability lawsuit, or it can serve as evidence of a company's knowledge of a defect in a civil lawsuit, which may be used by a plaintiff to persuade the jury that the FDA endorses the plaintiff's claim [13].

FDA warning letters and consequences of FDA warning letters and failure and associated costs

Consequences of FDA Warning Letters are generally in two categories. First are regulatory actions that are associated with the failure to correct the violations. Second is public disclosure of the existence of a 483 or Warning Letter. Public disclosure of FDA findings is allowed under US law. This disclosure negatively impacts company stock value, trust in the firm, and loss of sales from patients and healthcare professionals [14].

The cost of these oversights by industry has a huge economic impact on the medical device industry, and ultimately the consumer who may need a medical device. The estimates indicate that each year FDA Form 483 and warning letters and consent decrees along with associated warranties and lawsuits cost the industry between $2.5 billion and $5 billion US dollars on average. Another $1 billion to $ 2 billion is lost in sales of new and existing products [5,15].

There are costs associated with receiving an FDA action such as an FDA Warning letter. There are three different categories of potential costs: hard costs, soft costs, and hidden costs.

There are the Hard Costs, these include Compliant Handling and field service rework, Warranty Repairs, replacements, partner retraining, Consulting fees, and internal man hours associated with rework.

The Soft costs were listed as Patient Harm, Opportunity costs of device recalls, Product Liability, regulatory, and litigation costs, net cost of scrap and expired product, and delays in go-to-market timelines.

The Hidden Costs were listed as Lower valuation and reduced brand equity, difficulty recruiting and retaining top talent, and an internal culture of poor quality [16].

It is important to remember that, typically, a medical device manufacturer has one shot at success once it hits the market. If anything goes wrong, it can be extremely challenging, if not impossible, to fully recover from a damaged perception [16].

Nonroutine external quality failures represent 1.9 to 2.5 percent of annual sales. These costs result from significant quality and compliance events, such as recalls, warning letters, consent decrees, import bans, and consumer litigation. The cost of these events was estimated at $7 billion to $8.5 billion per year. Indirect costs such as revenue loss and market-cap impact related to non-routine quality failures can reach $1 billion to $3 billion for a medium to large company. These quality failures may lead to a major compliance action, such as a consent decree requiring a plant shutdown, which can have a disproportionate cost impact [15].

The manufacturer can easily spend hundreds if not thousands of hours of remediation, training, process implementation, and meetings. These costs alone can easily run to more than $250,000. One manufacturer estimated that they spent more than $5 million to make corrections at all 40 of his firm's sites [17].

Impact on approvals- when a Warning Letter is issued any pending approvals will be put on hold pending the outcome of the FDA action. This can cost a company money in lost market share and delay the product from being released or even being approved [17].

Competitive Response: in many cases, competitors will use this information to attempt to gain business and leverage the opportunity while the firm's products are not available in the market [17].

Loss of business can occur depending on the severity of the warning letter. Business entities may cancel, postpone or delay purchasing the firms' products pending the outcome of the FDA action. Also, damage to the firm's reputation could cause end users to switch to other vendors or simply cease ordering the product [17].

An example of this occurred in 2021 Medtronic received an FDA warning letter following a facility inspection. Medtronic's stock fell more than 9% after receiving the warning letter. Along with the stock hit, the company was downgraded by several Wall Street firms. Wells Fargo and J.P. Morgan lowered their ratings due to the warning letter. At the same time Medtronic's rival for a similar product, Tandem Diabetes Care stock rose 10.5% [18].

The cost of these oversights by industry has a huge economic impact on the medical device manufacturer, and ultimately the consumer who may need a medical device.

It is estimated that each year events such as FDA Form 483 issues, recalls and FDA Warning letters and consent decrees, along with associated warranties and lawsuits cost the industry between $2.5 billion and $5 billion per year on average, plus another $1billion to $2 billion in lost sales of new and existing products [5].

Literature Review

CAPA in the literature

Over the years many authors have attempted to help medical device manufacturers to find a way to implement an effective CAPA system that meets FDA requirements. But despite all the guidance in the regulations access to the FDA QSIT CAPA issues still dominate and are the most frequently cited inspectional observation. While many of them have given good advice it would be safe to assume that the medical device industry still fails to understand the CAPA process based on the number of FDA Warning Letters citing CAPA issues [19].

CAPA has been a major stumbling block for many companies, mainly in manufacturing operations. About 50% of FDA 483s seen in the industry relate to CAPA–the highest single category of FDA non-compliance. Therefore, the FDA does a thorough check during every inspection it performs in a company. If companies know that CAPA is a major non-compliance issue, why are they not taking adequate safeguard measures? Opinion is that current CAPA measures are failing because CAPA is often considered a compliance need rather than as an important mechanism to improve operational excellence [20].

Effective CAPA management will not only save manufacturers in compliance audits, but its preventive measures can also help manufacturers improve productivity by radically reducing rework. Effective CAPA management could bring on-time analysis of process execution data to identify deviations and take early action to improve quality and productivity. CAPA needs to be viewed with a broader outlook and made a key focus area for corporate, away from the traditional view of a point-in-time localized function. Manufacturers can get substantial benefits by taking an enterprising view of CAPA [20].

Many companies have simply not paid enough attention to the CAPA process. It has been suggested that CAPA should be a main part of the company compliance process. And that the improvements achieved through CAPA should be implemented company wide. Creating a good quality system benefits the organization and assists in developing a product that meets both customer and FDA approval [20].

Many medical device manufacturers fail to prepare a good approach to their CAPA process, which is important to the health of the company. Generally, there are five most common problems with the CAPA process. These are: lack of cross-functionality, reactive instead of proactive, overuse versus underuse, poor root cause determination, and a poor definition of a CAPA process [19].

Many manufacturers fail to realize that a CAPA is seldom an issue that only impacts the quality function. A CAPA is almost always cross-functional in nature, involving many groups and functions within the manufacturer. Additionally, CAPA is a project that will require resources from throughout the company. CAPA many times are not treated as equal to other company initiatives. This is one of the reasons how and why CAPAs linger and are ultimately ineffective [19].

As for being reactive instead of proactive, most companies are more inclined to address known problems than to invest resources in preventing problems. Companies need to have systems in place to access and identify issues before they become problems. Also, companies tend to do two extremes either overuse or underuse the CAPA process [19].

There are CAPA tips to help implement an effective process. The goal of this advice is that it is essential that medical device manufacturers develop the right system from the beginning to ensure QMS effectiveness and minimize or eliminate the risk of having issues with the FDA or other regulatory bodies [21].

Global manufacturers need to detect issues at all levels of the company to conduct efficient and timely continuous improvements in their operations to eliminate the causes of non-conformities or other undesirable situations. In a large global company, it is even more important to have an effective CAPA system because often issues are detected by various units in a company that may have a wider negative effect [22].

While there appears to be a wealth of literature and guidelines out there it appears that a fundamental lack of knowledge still exists on how to effectively manage a CAPA. In the United States, the FDA makes available to the public the QSIT manual which outlines the exact items that will be reviewed. The FDA also makes publicly available the Inspection Operations Manual (IOM) which details the inspection process that FDA Investigators must follow [19].

In the review of the literature most all the authors address the regulations or give their preferred method for making a CAPA work. However, no author addresses the fundamental issue relating to the specific causes of FDA 483 citations. More directly what are the specific issues that lead to the manufacturers failing CAPA inspections.

The biggest challenge that medical device companies face in implementing and documenting CAPAs is achieving an organizational culture change. The challenge is that it will require medical device companies to mitigate where quality is responsible for everything, to a culture where senior management is totally enrolled in the program, and totally understands, supports, and takes ownership of the system. Without that level of involvement from senior management, it will be a challenge [23]

The history of FDA CAPA-related issues

The FDA requires medical device companies to have clearly documented procedures for CAPA. Unfortunately, many medical device companies fail to provide a good approach to their CAPA process. By neglecting this key area companies are putting the health of their company at risk [19].

Problems with medical device companies and CAPA-related issues are nothing new. Since the FDA implemented the QSIT in 1999, CAPA-related issues have been a constant problem. A study conducted from 1997-2007 CAPA CAPA-related issues were the number one source of FDA Warning Letters [24].

A study conducted examining FDA Warning Letters issued in 2009 and found that CAPA-related issues were the number one source of them [25]. A study of FDA-related warning letters from 2013-2019 and found that approximately 58% of all FDA Warning Letters cited one or more CAPA-related violations [4]. A study in 2021 showed that this trend held true and that CAPA was once again the most cited violation [26].

The COVID years 2020-2021 were years during which the FDA essentially shut off routine facility inspections. As a result, the FDA wasn't generating inspectional results that would lead to a warning letter.

CAPA improvement ideas

As evidenced CAPA has been and continues to be a significant problem for the medical device industry. While CAPA is critical to eliminate systemic problems during manufacturing and ensure that they don't recur many companies struggle with their CAPA systems [27].

A 2022 Survey that consisted of 519 participants, of whom are employed in quality, product development, and executive management positions by device organizations ranging in size from small to enterprise-level that are located in various regions around the world found that only 17% of the participants felt that they had achieved excellence, 33% said they were above average, 38% said they were average and 7% stated they were below average and 3% felt that their company did a very poor job with CAPA [27].

It has been stated there are five causes for problems with CAPA. They Lack cross-functionality, are reactive instead of proactive, overuse vs. underuse, have poor root cause determination, and poor definition of a CAPA process [28].

A four-prong approach was suggested that for a company to get traction in their CAPA they needed to: Gain organizational commitment, integrate root cause analysis into the quality systems, train key people, and provide reinforcement and tools [29].

Medical device companies fail to remember that there are several required inputs into the CAPA system. This could lead companies to create an early warning system through internal audits. The manufacturer should that look at both internal and external data sources to find areas of concern. Specifically,

the company should look at process control data, Test/Inspection data, Device History Records, Internal Audits, Nonconforming material reports, rework and scrap/yield data, training records, supplier controls, complaints, customer feedback, servicing repairs, Adverse Event Reports (MDR), FDA bulletins and other communication and information from similar competitor devices [30].

Companies didn't integrate risk analysis and risk management into CAPA and made it part of their company's quality system. Companies should ask themselves two questions when deciding how to evaluate the risk of each CAPA. This would involve answering two questions: Does the CAPA issue relate to an essential output? Does the CAPA issue appear in the risk analysis? [31].

Missing and inadequate CAPA procedures have been the top cause of warning letters for over a decade. The company should take time to create a complaint CAPA procedures document that details the guidelines for your organization's approach to CAPA [32].

CAPA procedures should define the objectives, criteria, steps and responsibilities of the CAPA system and should contain: An overview of the CAPA procedures, including scope, purpose, involved personnel, and list of external resources referenced in the document, Definitions of terms like "corrective action", "incident", or "non-conforming product", CAPA Process Flow, which lays out steps to the CAPA process and how it advances through each phase. CAPA forms are to be filled out when events occur, and the investigation proceeds to serve as your documentation of the process. Additional information explaining the role of management in the review process [32].

The operative goal of a CAPA system is to create CAPA responses that are simple, non-technical, easy to understand terms and increase satisfaction by ensuring precise and timely CAPA. The model suggested is known as the CAPA 5C model. The main elements of the CAPA C5 model are as follows: condition (the physical state in which failures exist), cause (the producer of an effect or condition), correction (the act of accurately correcting bad conditions), communication (the activity of exchanging information and thoughts) and cost (the outlay, expenditure, and penalties incurred in achieving the correct situation) [22].

CAPA should be divided into two streams: External Events & High-Risk Trends and Internal Events & Low-Risk Trends. The framework proposes that external issues be managed through the traditional CAPA process because they would be issues warranting increased attention, whereas internal issues could be managed through existing subsystems within a quality management system [33].

The external flow aims to apply more rigor in critical thinking to identify the root cause (or underlying cause) of the nonconformity, implement investigation decisions, and verify or validate effectiveness. The internal flow includes medium and low-risk trends that can be addressed through existing subsystems within the quality system by using a fast-track, or streamlined, CAPA process [33].

It has been proposed that the medical device industry adopt the Six Sigma method. The practice of designing quality into a product is often misunderstood. Too often, medical device companies who plan for designing quality into a product are focusing on safety and reliability. While these qualities are obviously important, it is more important for companies to understand that quality does not simply mean defect-free products but includes meeting customers' needs [34,35].

Adopting Six Sigma helps improve CAPA system compliance performance. Using the Six Sigma approach helps in defining the bottlenecks as well as different sources of variations within a CAPA process [34].

Given the reputation for reliability in the automotive and aerospace that the Eight Disciplines (8D) model should be looked at. The 8D model works by alternating inductive and deductive problem-solving steps to identify a root cause and work toward a resolution. This can be done in several ways, but typically includes data-driven tools and analysis for inductive activities and an individual or group of subject matter experts to deduce results. The 8D positions verification of corrective actions before implementation. This system unfortunately would cause problems for the medical device company because the FDA requires manufacturers to verify that actions, they took to correct a problem were effective at doing so. The FDA regulations state that it's not enough to simply verify that they were implemented [36].

Discussion

Currently, there is no specific guideline or model on how to design and create an FDA-compliant CAPA system. This is one of the reasons that medical device companies struggle with implementing FDA regulations and requirements concerning the CAPA system [34].

The FDA does not dictate the degree of action that should be taken to address a quality problem, but it does expect companies to have a plan in place. It expects companies to address how they will perform their investigations, how they determine probable root cause or causes, and how they will implement corrective action [37].

The CAPA process has become highly focused on compliance. Moreover, medical device companies struggle to determine which issues require a more structured CAPA process and which can be solved in alternative ways. So many medical device companies take a "one size fits all" approach and open the formal, structured CAPA process for most issues. What's worse, the fear of findings by the FDA leads companies to spend a lot of time on paperwork, often slowing down the effects of addressing issues. The cost just to maintain the paperwork flow could be around 1% of the company's revenue [33].

However, companies have a legitimate fear of failure of a regulatory inspection. Quality issues rightly concern every stakeholder in the medical device value chain, from manufacturers and regulators to payors, doctors, and patients. Media attention has increased, and investors have severely punished some companies with quality issues. In the past decade, the average of one company per year has seen a 10 percent drop in price after a single, major quality event (e.g., a major product recall). Indeed, the risk that a major quality event will cause serious long-term value destruction is high and rising. The economics of quality are uncertain, in part because consumers and other stakeholders are not always able to recognize or reward superior quality. Regulatory approval sets a baseline and is often the only objective measure of medical device quality [5].

Also, few companies use sophisticated reliability engineering practices such as accelerated life testing analysis, life data, or failure analysis routinely used in the automotive and aerospace industries for product development and process controls. Many medical device companies are small and lack resources or experience in developing risk assessment or mitigation plans during the development phase. This impacts their ability to monitor or control quality through manufacturing and post-production [5].

One of the biggest challenges for medical device companies is to understand the fundamental requirements of the FDA. Despite the FDA clearly outlining their expectations under CFR 820.100 and further outlining exactly what and how a CAPA will be evaluated. Despite the QSIT being used in all medical device inspections since 1999 there still exists the problem of CAPA-related violations constantly being one of the most cited medical device Warning Letter findings. To the FDA the CAPA system is seen as the determining factor of the overall health of a company's quality system. The FDA considers CAPA to be an extremely important part of every medical device inspection and will be examined [4,37].

While there are numerous theories about what is the best approach to a quality CAPA system it is hard to determine which one offers the best solution. Most approaches can be scaled to work for a wider range of companies from large too small. Others require complex systems and subject matter experts to run them.

The key is to understand the expectations of the FDA when it comes to CAPA. Your system can incorporate any number of ideas or combinations of them to make sure that the medical device company understands the specific

requirements of all nine subparts of CFR 21 820.100. Failure to have a system or process that covers all these areas will result in potential FDA actions. Each part has individual elements and requirements that are specific.

By examining all the nine parts of 21 CFR 820.100 and outlining the compliance requirements for each and examined a time period of 2013-2019 Warning Letters with a detailed breakdown by number and percentage of all violations. This gives insight to verify if your CAPA system meets the elements of each subpart that the FDA expects to see [4].

Examining the FDA data from 2020 inspections and found that 197 times CAPA were cited, the medical device company either did not document or cite procedures. Roughly 83% of the CAPA citations indicated that the company didn't have procedures documented [26].

Just putting down a procedure assumes that you have a procedure. Most of the companies cited didn't have a procedure so if you don't have a procedure how would you document something you don't have? And just because you have a procedure, doesn't necessarily mean it works. If the medical device company still hasn't defined its process and procedures on things like CAPA that is of serious concern. The elements are well defined with CFR Part 820 and have been in existence since 1999 [26].

Conclusion

The paper covered the costs and insight into some possible solutions for medical device related CAPA issues. The problems are huge in that medical device companies' year in and out still fail to meet the FDA expectations for CAPA.

The issues that have been cited by the FDA are clearly defined in federal regulations and the FDA is considered the most open and transparent regulatory agency. All FDA medical device inspections follow the QSIT. This document is over 100 pages long and clearly outlines the FDA areas of emphasis and what the expectations are for that.

Not enough companies understand the FDA's expectations on CAPA. Approximately 72% of the medical device warning letters from 2013-2019 were for failure to comply with the basic element of 21 CFR 820.100 the requirement that medical device companies establish and maintain CAPA procedures. This time period is only a snapshot of the ongoing problems that occur each year in and out.

Until medical device companies understand and make their CAPA meet the FDA guidelines they will continue to spend large amounts of money to correct these issues. Additionally, they put themselves at risk for lawsuits, loss of market share, and in extreme cases that product must be recalled or removed from the market.

Investment and understanding the FDA CAPA requirements are essential to maintaining and keeping their companies viable. Also, there is a human cost that needs to be included. A significant number of medical devices are implantable and would require additional surgery to remove a defective product. This gives rise to lawsuits and liability and a negative public image of the company and product.

Research Limitations/Implications

This study only looked at CAPA-related FDA Warning Letters and associated costs in the US Medical Device industry. The FDA has specific guidelines that only apply to medical devices bought, sold, or imported into the US Market. Since the US Market is roughly 40% of the global market for all medical devices it is the largest single market in the world.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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