

# FDA Medical Device Warning Letters and Trends Pre and Post COVID 2013-2022

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## Abstract

The United States Food & Drug Administration requires under Title 21 of the Code of Federal Regulations (21 CFR) Part 820.100, that medical device manufacturers must establish a system to address Corrective And Preventive Actions (CAPAs) to meet regulatory standards. This article provides insight into medical device quality issues relating to CAPA through the evaluation of warning letters issued by the US Food and Drug Administration (FDA) between 2013 and 2022. The results of this study indicate that despite the medical device regulations being in place since 1976 violations of 21 CFR 820.100 (CAPA related violations) continues to be a significant issue for medical device companies.

**Keywords:** CAPA • CDRH • FDA • Warning letter

## Introduction

The United States Food and Drug Administration (FDA) is a federal government agency that is responsible for safeguarding public health in the United States. The agency has a wide mandate to ensure the safety of pharmaceutical drugs, biologics, medical devices, animal drugs, cosmetics, food and radiation emitting products [1]. To ensure the safety and quality of these products the FDA investigates companies for their regulatory compliance through inspections.

The study's goal was to evaluate warning letters issued by the FDA and identify and understand the nature of violations that occur related to medical device Corrective and Preventive Actions (CAPA). An analysis was performed on warning letters issued by the center for devices and radiological health, office of medical device and radiological health operations and division of medical device and radiological health operations in the years 2013-2022. The analysis gives an overview of the major categories of objections as well as a better understanding of FDA expectations during an inspection of the medical device industry. This includes a breakdown of specific CAPA related regulations and FDA expectations, an outline the areas of 21 USC 820.100 that are frequently found to be violated. The study will look at the effect on FDA Warning Letters based on pre-COVID (2013-2019) and post-COVID (2020-2022)

## Corrective and Preventive Action (CAPA)

CAPA is the key regulatory focus during an FDA medical device inspection. The FDA will review it in the following situations. (A) During a medical device inspection, the FDA Investigator will follow the Quality System Inspection Technique (QSIT), Corrective and Preventive Action (CAPA) subsystem (B) When doing an inspection under Compliance Program Guide 7382.845, Inspection of medical device manufacturers (C) Premarket Approval Applications (PMAs) will review CAPA in the original PMA and some PMA

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supplements (Site changes, 30-day Notices) (D) During a recall (corrections and removals). The FDA will not review CAPA during the 510(k)-application process [2].

The FDA defines CAPA under 21 USC 820.100. This regulation requires that each manufacturer establish and maintain procedures for implementing corrective and preventive actions. Eight specific subsections of 21 CFR 820.100 define the exact requirements that must be met during each inspection [3].

In the FDA QSIT guide, they define the purpose of CAPA as, the purpose of the corrective and preventive action subsystem is to collect information, analyze information, identify and investigate product and quality problems and take appropriate and effective corrective and/or preventive action to prevent their recurrence. Verifying or validating corrective and preventive actions, communicating corrective and preventive action activities to responsible people, 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. One of the most important quality systems elements is the corrective and preventive action subsystem [4].

## Warning letters

FDA Warning Letters are notifications issued to manufacturers found to be in significant violation of federal law. Warning letters represent serious regulatory violations and require prompt corrective action from the recipient. The most common causes of Warning letters are non-compliant written procedures, failure to follow written procedures and failure to prove that regulations have been followed and adequately documented [5,6].

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 issued only for violations of regulatory significance meaning that they may lead to enforcement actions if corrective actions are not taken. Failure to resolve an FDA warning letter could result in a Consent Decree which is a legal agreement between the company and the FDA. It is a negotiated agreement detailing voluntary actions pledged by the affected company to remedy nonconformances, including systems improvements to avoid FDA litigation. Failure to adhere to these conditions will result in a referral to the United States Attorney's Office for further legal action. Additionally, the FDA can request a seizure which is an action against a product that is adulterated and or/ misbranded. This action removes violative products from commerce. The escalation can continue with an injunction which is a court ordered action brought by the FDA that requires a company or individual(s) to refrain from a specific action. The most severe action can be in Criminal Prosecution and Fines that are levied against the company or individuals [5-7].

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 manufacturers to take prompt action. The FDA Warning Letter has several potential legal ramifications such as, the FDA can decide to take regulatory action, may be introduced as evidence in a product liability lawsuit, may serve as evidence of a company's knowledge of a defect in a civil lawsuit, may be used by a plaintiff to persuade the jury that the FDA endorses the plaintiff's claim [6,7].

Like FDA Form 483 Observations, Warning Letters require a response within 15 working days. The response should include immediate acknowledgement of receipt of the letter, creation of a Corrective and Preventive Action plan (CAPA), provision of a timeline to the FDA if corrective action will take more than 15 business days and implementation of the plan prior to a follow-up inspection [6].

A primary goal of the company should be to reassure the FDA that the product or practice in question is safe and effective, so all responses should be crafted with this in mind. It should be straightforward and clearly demonstrate how the issues raised in the FDA warning letter will be corrected. Unsupported claims should be avoided in response to an FDA warning letters. The quality and thoroughness of the FDA warning letter response may help determine whether or not escalation to further regulatory or legal action is necessary [6]. In the current study, the objective was to evaluate warning letters to identify and better understand FDA expectations related to medical device CAPA issues. The analysis identifies the major categories of these objections to better understand the FDA expectations during an inspection.

## Methods

To identify and evaluate CAPA issues in medical devices, this study adopted a methodical process of data collection, categorization of violations and trend analysis for interpretation of results. Data collection consisted of the extraction of violations of 21 CFR 820.100 and subsections of this regulation. All data for warning letters were collected from the public database available on FDA's website [8]. The list of warning letters from 2013-2022 were then reviewed focusing on the issue date, issuing office and subject of the warning letter. Screening of these warning letters was performed to include only those that referenced one or more violations related to medical device CAPA issues. Only those letters that related to medical device CAPA were reviewed. The text of each letter was reviewed to identify the specific violation(s) over the study period. Warning letters selected included those issued by the FDA Centers for Devices and Radiological Health, Office of Medical Device and Radiological Health Operations and Division of Medical Device and Radiological Health Operations (Table 1).

## Results

In the Pre-COVID era 2013-2019 a total of 355 CAPA related Warning Letters were issued by the FDA. A total of 34 Warning Letters contained more

than one CAPA violation. During the Post-COVID era a total of 35 CAPA related warning letters from 2020-2022 were reviewed with a total of 37 violations identified (Table 1). A total of 2 warning letters contained more than one CAPA violation [8].

Since the regulation relating to CAPA contains several subparts, the following breakdown of each subsection will help identify the elements of each subsection of 21 CFR 820.100.

### 21 CFR 820.100(a)

This section requires that the medical device company establish and maintain procedures for implementing corrective and preventive action. The procedures (for implementing corrective and preventive action) must provide for control and action to be taken on devices distributed and those not yet distributed, that are suspected of having potential nonconformities [5,9,10].

**21 CFR 820.100(a) (1):** This section requires that analyze 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.

The section refers to the CAPA Analyze Phase. Product and process issues are identified in many ways including customer complaints, product defect reporting, quality or process deviations or exceptions, signals management and adverse reporting etc. Inadequate responses to managing these issues, in particular customer complaints and not performing robust risk analysis against them are common causes of this issue. It is important to show that the medical device company to be able to provide evidence that the organization has handled and corrected the issue sufficiently. It is important to have a central repository such as a document management system to act as the source of product, process and quality issues. A document management system allows the medical device company to have a single source of truth. Additionally, it allows you to transparently supply evidence, on demand, that all issues/signals were identified, triaged and analyzed for risk [3,9,10].

**21 CFR 820.100(a) (2):** This section requires that investigate the cause of nonconformities relating to the product, processes and the quality system. This section refers to the CAPA Investigation Phase. This section requires the CAPA investigation phase to complete a comprehensive Root Cause Analysis of any issue signal judged significant and resulting in one or more CAPAs during the analyze phase. The goal is to identify the causes of undesired outcomes, such as behaviors, actions or conditions that must be corrected to prevent recurrence. The analysis must consider quality systems and processes. The issues are often multi-dimensional and caused by a combination of root causes. To be effective, the analysis must go beyond the symptoms of the issue or problem to identify all potential root causes [3,9,10].

**21 CFR 820.100(a) (3):** This section requires that identify the action(s) needed to correct and prevent recurrence of non-conforming product and quality problems. This section refers to the CAPA Identification Phase. This section meets the regulatory requirement to identify and capture all CAPA actions necessary to address and prevent the causal factors identified in

**Table 1.** Summary of CAPA warning violations by 820.100 section pre and post COVID.

CAPA820.100(A) 1 thru 7 and (b) Sections	Pre-COVID	Post-COVID
820.100 (a) Establish and Maintain Procedures	293	35
820.100 (a) (1) Analyzing the Quality Problem	34	1
820.100 (a) (2) Investigating the cause of Failure	8	0
820.100 (a) (3) Identifying the action for CAPA	9	0
820.100 (a) (4) Verify and Validate CAPA	18	0
820.100 (a) (5) Implementation of CAPA	1	0
820.100 (a) (6) CAPA related Communication	1	0
820.100 (a) (7) Management Review of CAPA	0	0
820.100 (b) CAPA related documentation	43	1
Total Number of Violations	407	37
Total Number of Warning Letters	355	35

the investigation phase. The CAPA plan must clearly define each action and explain how it corrects or prevents recurrence of the problem and issue. CAPA actions should be sustainable, practical solutions to a non-conformity and that their implementation is time bound [3,9,10].

**21 CFR 820.100(a) (4):** This section requires that verify or validate the corrective and preventive action to ensure that such action is effective and does not adversely affect the finished device. This section refers to the CAPA Verification Phase. Verification addresses whether a product or a process meets the intended use or requirements. Verification assures that there is quality in the process or building of the product itself. CAPAs require verification and validation that both the original issue was addressed and that no other quality issues were introduced in the process [3,9,10].

**21 CFR 820.100(a) (5):** This section requires that implement and record changes in methods and procedures needed to correct and prevent identified quality problems. This section refers to the CAPA Implementation Phase. This section requires that you execute the CAPA implementation. This can include making planned process and quality changes. Keeping evidence of their implementation. Documentation, as part of implementation, may include new or updated implementation plans, change management records, SOPs, specifications and training plans etc [3,9,10].

**21 CFR 820.100(a) (6):** This section requires that disseminate information related to quality problems or nonconforming products to those directly responsible for assuring the quality of such product or the prevention of such problems. This section refers to the CAPA Dissemination Phase. Dissemination addresses communications, regulatory reporting, training, retooling where appropriate, modifying responsibilities and management accountability. Dissemination is the requirement to communicate information on the CAPA, including parties throughout the lifespan of the CAPA [3,9,10].

**21 CFR 820.100(a) (7):** This section requires that submit relevant information on identified quality problems, as well as corrective and preventive actions. This section refers to the CAPA Management Review Phase. The management review phase, like the dissemination phase of the CAPA, spans the process end to end. This addresses the requirement that senior levels of management provide CAPA oversight, sign-off on risk severity and action plans and routinely monitor progress against the plan, as well effectiveness metrics and outcomes [3,9,10].

## 21 CFR 820.100(b)

This section requires that the medical device company document all activities required under this section and their results. The section relates to the CAPA documentation phase. It is a requirement to create and preserve objective evidence. The existence of a well formed, well documented CAPA system is critical to a regulator's assessment of a medical device companies seriousness in addressing quality issues/signal and risk management.

## COVID-19-related warning letters

In March 2020, FDA decided to postpone its inspections except for mission critical inspections work [11]. During the COVID-19 pandemic which covered the years of the study, many warning letters issued were related to COVID products. Between 2020 and 2022 approximately 65 medical device warning letters were issued specifically to COVID related products. In most cases these warning letters were for unapproved and misbranding of COVID-19 products [8]. These warning letters did not contain any CAPA related findings but skewed the number of warning letters issued during this time frame.

## Discussion

Most medical device companies want to avoid FDA warning letters. By identifying these violations that might lead to CAPA related warning letters provides an opportunity to identify and remedy these areas prior to an FDA inspection. The FDA uses the Quality System Inspection Technique's (QSIT) Guide to Inspections of Quality Systems. The QSIT provides instructions to FDA Investigators conducting medical device quality systems inspections [4]. The QSIT is used in conjunction with the FDA Compliance Program Guidance

(CPG) manual Inspection of Medical Device Manufacturers (CPG 7382.845) [12].

The inspectional objectives for a CAPA are outlined in the QSIT. The FDA considers the CAPA system as one of the most important quality systems for inspection. The CAPA system is mandated to be checked during a Level 1 abbreviated inspection (CAPA plus one other system) for companies who are compliant (i.e., the company has no warning letters or other regulatory issues with the FDA). Also, for surveillance inspections, it will always start with the CAPA system [2].

CAPA is critical to eliminate systemic problems during manufacturing and ensure they don't recur. A 2022 industry survey of over 500 leaders in the global medical device industry found that many organizations report mediocre CAPA systems and competency. The research showed that approximately half of those surveyed say that their company's level of competence is an average of below. Just 17% say they have achieved excellence with CAPA. The numbers show that 33% felt they were above average, 38% average and 7% below average and 2% of the individuals surveyed said they would rate their company as very poor [13].

A study that looked at the number of CAPA related categories from 2013-2019 found out of a total of 407 medical device Warning Letters that 21 CFR 820.100(a) establishing and maintaining procedures was the topmost cited violation (293 citations). Followed by 21 CFR 820.100(b) CAPA related documentation (43 citations) and 21 CFR 820.100(a)(1) analyzing the quality problem (34 citations) [9]. Post-COVID 21 CFR 820.100(a) resulted in the highest number of violations (35 citations) [8]. The low number of Warning Letters from 2020-2022 were also a result of the years 2020 and 2021 during the COVID years which FDA essentially shut off routine facility inspections. As a result, the agency wasn't generating inspectional results that would lead to a Warning Letter. Instead, many of the Warning Letters stemmed from such issues as unapproved laboratory tests for COVID and adulterated personnel protective equipment, not based on a specific FDA facility inspection [14].

During the Pre and Post COVID eras, the most cited violation was 21 CFR 820.100(a) which requires that medical device companies Establish and maintain procedures for implementing corrective and preventive action [3,9,10]. This is not new news. A study conducted in 2010 reviewed FDA Warning Letters issued in 2009 and found that there were more violations of 21 CFR 820.100(a) than any other finding. Between 2013 and 2019 this pattern held similar results. The number of violations of 21 CFR 820.100 (a) averaged approximately 58% of total medical device Warning Letters issued between 2013 and 2019 [9].

The FDA has in the past few years reduced the number of overall warning letters issued. The FDA considers benefit-risk factors and a company's compliance history when determining whether to issue a warning letter. Over the past decade or so, FDA Center for Device and Radiological Health (CDRH) has also been shifting how it communicates with medical device companies, focusing on pushing companies to prioritize making decisions that improve quality and patient outcomes rather than simply achieving compliance with regulatory requirements. The goal is to have companies address potential issues before they rise to the warning letter stage [14-17].

## Conclusion

The study offers a detailed analysis of warning letters issued by CDRH to medical device manufacturers from 2013-2022. The study showed that the largest number of warning letters were issued for the most fundamental of the CAPA regulations 820.100(a) the requirement that requires that a medical device company establish and maintain procedures for implementing corrective and preventive actions. A lack of understanding of this requirement would cause an FDA investigator to question and probe further into the medical device company's understanding of the CAPA system. To an FDA Investigator failure on the part of the company to understand this concept could weigh in on determining the overall health of the medical device companies quality systems. Warning letters can be an important source of data to study and analyze CAPA-specific violations that occur in the medical device industry.

The FDA does not dictate how a medical device company addresses the quality issue but rather that there is a plan in place and that it is robust enough to detect and remedy quality related issues. A review of the warning letters shows that the FDA closely monitors the quality systems of a medical device company and the quality unit. Overall, the study emphasizes that to have a smooth inspection or PMA a medical device company should focus on the CAPA system and keep themselves updated with current FDA related guidance's to be aware of the expectations and by reviewing and understanding studies like this what the current thinking of the FDA is.

And while the number of overall medical device Warning Letters have dropped over the years the FDA is still conducting inspections and finding CAPA related violations. Based on the review of 2013-2022 it shows that CAPA remains an issue of regulatory concern and that the FDA will continue to examine the CAPA system in every inspection and still find issues.

## Limitations

The analysis was performed only on warning letters issued by the Center for Devices and Radiological Health, Office of Medical Device and Radiological Health Operations and Division of Medical Device and Radiological Health Operations for the years 2013-2022. Regulatory enforcement strategies change and evolve so this study is representative of the FDA enforcement strategy in place at the time the actions were generated.

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## 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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