# Analysis of FDA warning letters issued to US medical device companies for CAPA related issues between 2013 and 2019


## Abstract for marketing purposes

*According to Title 21 of the Code of Federal Regulations (21 CFR) Part 820.100, medical device manufacturers must establish a system to address corrective and preventive actions (CAPAs) to meet regulatory standards. In this article,* ***Randy Anderson*** *and* ***Christabel Tan*** *provide 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 2019. The results of this study indicate that despite the Quality System Inspection Technique being in existence for over 23 years and numerous articles citing violations of 21 CFR 820.100, there continues to be significant inadequacies in how medical device companies use the CAPA system.*


## Introduction

The regulatory gap between the actions of medical device companies and the expectations of the US Food and Drug Administration (FDA) is seen through violations captured in issued warning letters. Many violations of Title 21 of the Code of Federal Regulations (21 CFR) 820.100 are evident through findings reported in warning letters. The identification and analysis of violations of 21 CFR 820.100 gives critical insight into the FDA's current thinking on medical device regulation and suggests medical device manufacturers need to strengthen their CAPA systems to ensure compliance with FDA regulations. An ineffective CAPA system impacts a business' bottom line and, more importantly, affects patients who receive the devices or may require one later. Frequently, a medical device company is required to recall a device or take it off the market temporarily.

An FDA warning letter is an escalation of compliance enforcement by the Agency. Warning letters place mandatory requirements on a medical device company. FDA warning letters are also publicly available on the FDA website.

For medical device companies that have pre-market applications for Class III medical devices, the FDA will withhold approval until all violations have been corrected. Serious violations coupled with product safety concerns can also trigger an FDA product recall. Additionally, the FDA may escalate past the warning letter and take immediate action if it determines that the violations could lead to a reasonable possibility of injury or death[1,2].

## Historical background

Prior to 1976, the regulations were aimed at food, drugs and cosmetics, and for medical devices they were either vague or not applicable. The *Medical Device Amendments of 1976* required for the first time the use of general controls that applied to all medical devices. The rules required all medical device manufacturers to adhere to Good Manufacturing Practices, and authorised the FDA to inspect factories which manufactured medical devices and their records[1].

In August 1999 in response to industry and Congressional inquiries and concerns, the FDA released the Quality System Inspection Technique's (QSIT's) *Guide to Inspections of Quality Systems*[3]. The QSIT provides instructions to FDA investigators conducting medical device quality systems inspections. It is used in conjunction with the FDA Compliance Program Guidance Manual entitled *Inspection of Medical Device Manufacturers* (7382.845)[4]. This manual was prepared by the Office of Regulatory Affairs and the Center for Devices and Radiological Health (CDRH), and provides guidance for FDA inspection of medical device manufacturers against the Quality System Regulation (21 CFR 820) and related regulations.

The inspectional objectives for a CAPA system are detailed under the Corrective and Preventive Action section of the QSIT. When an FDA inspector begins an inspection, the Compliance Program Guidance Manual serves as a guide to conducting this area of the inspection. The FDA considers the CAPA system as one of the most important quality systems for inspection. Much of an FDA investigator's time will be spent examining this one section of the QSIT[3,4].

When the FDA does a follow-up inspection, it has the mandate to establish a Level 1 Abbreviated Inspection (CAPA plus one other system) for companies who are compliant (i.e. the company has no warning letters or regulatory issues with the FDA). Also, for surveillance inspections, it will always start with the CAPA system[3,4].

## Warning letters

Warning letters are issued by the FDA to notify of significant regulatory violations of the Federal *Food, Drug and Cosmetic Act* made by medical device companies. A warning letter is important because it identifies the need for prompt corrective action and gives the medical device company the opportunity to take voluntary action before enforcement action is taken[2].

Before the issuance of a warning letter, an inspection is conducted by an FDA investigator. Any observations made during the inspection are noted in FDA Form 483. Once a medical device company receives an FDA Form 483, it is encouraged to respond to the FDA with an appropriate corrective action plan within 15 working days[5,6]. If this requirement is not met due to unresponsiveness or an insufficient response, a warning letter is issued as an escalation from the FDA


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Form 483. A warning letter is far more serious than an FDA Form 483 and the medical device company implementation of corrective action is required by law[5,6].

## Evaluation of CAPA issues

### Method

To identify and evaluate CAPA issues in medical devices, this study adopted a methodical process of data collection, categorisation 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.

The FDA database was searched for all warning letters pertaining to medical devices from 2013 to 2019; each warning letter that cited a violation of 21 CFR 820.100 was collected. Violations were categorised into the nine subparts of 21 CFR 820.100 as seen in Table 1 and totalled for the specified timeframe of 2013–2019. A trend analysis was performed by converting violation totals into percentages for each of the nine subparts. A total of 355 CAPA related warning letters were issued during that period resulting in a total of 407 violations. It is possible that warning letters can contain more than one violation. For the period covered, 34 warning letters contained more than one CAPA related violation.

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**Table 1. Summary of CAPA categorisations from 355 warning letters issued between 2013 and 2019**

| Subpart of 21 CFR 820.100 | Number of violations | Percentage of violations |
|---|---|---|
| 820.100(a) on establishing and maintaining procedures | 293 | 72.0% |
| 820.100(a)(1) on analysing the quality problem | 34 | 8.4% |
| 820.100(a)(2) on investigating the cause of failure | 8 | 2.0% |
| 820.100(a)(3) on identifying the action for CAPA | 9 | 2.2% |
| 820.100(a)(4) on verifying and validating the CAPA | 18 | 4.4% |
| 820.100(a)(5) on implementing the CAPA | 1 | 0.2% |
| 820.100(a)(6) on CAPA related communication | 1 | 0.2% |
| 820.100(a)(7) on management review of CAPA | 0 | 0.0% |
| 820.100(b) on CAPA related documentation | 43 | 10.6% |
| **Total** | **407** | **100.0%** |

### Results

## *Focus – CAPA Issues*

A total of 355 CAPA related warning letters from 2013–2019 were reviewed with a total of 407 violations identified (*see* Table 1). A total of 34 warning letters contained more than one CAPA violation. Since the regulation relating to CAPA contains several subparts, the following breakdown of each section in order of frequency of violations gives an overview of the areas of concern:

*21 CFR 820.100(a)*

This section accounted for the highest number of violations at 72%. It requires a medical device company to 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 non-conformities[7].

*21 CFR 820.100(b)*

This section relates to the CAPA documentation phase and accounted for 10.6% of the violations. It requires a medical device company to document all activities required under this section, and their results[7] (i.e. 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 company's seriousness in addressing quality issues/signals and risk management[8].

*21 CFR 820.100(a)(1)*

The CAPA analysis phase accounted for 8.4% of the violations. This requires the manufacturer to analyse processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned products, and other sources of quality data to identify existing and potential causes of non-conforming products, or other quality problems[7].

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 for a medical device company to be able to provide evidence that it has handled and corrected the issue sufficiently. It is also important to have a central repository such as a document management system to manage product, process and quality issues effectively. Using a document management system allows a company to supply evidence transparently, on demand, that all issues/signals have been identified, triaged and analysed for risk[8].

*21 CFR 820.100(a)(4)*

This section on the CAPA verification/validation phase accounted for 4.4% of the violations. It requires a company to verify or validate the corrective and preventive action to ensure that such action is effective and does not adversely affect the finished device[7]. 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[8].

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*21 CFR 820.100(a)(3)*

This section on the CAPA identification phase accounted for 2.2% of the violations. It requires companies to identify the action(s) needed to correct and prevent recurrence of a non-conforming product and quality problems[7]. This section meets the regulatory requirement to identify and capture all CAPA actions necessary to address and prevent the causal factors identified in 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 their implementation must be within a specified timeframe[8].

*21 CFR 820.100(a)(2)*

This section on the CAPA investigation phase accounted for 2% of the violations. It requires a company to investigate the cause of non-conformities relating to a product, processes and the quality system[7]. The CAPA investigation phase requires a comprehensive root cause analysis of any issue signal judged significant and resulting in one or more CAPAs during the analysis phase. The goal is to identify the causes of undesired outcomes, such as behaviours, 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[8].

*21 CFR 820.100(a)(5)*

The CAPA implementation phase section accounted for 0.2% of the violations. This section requires a company to implement and record changes in methods and procedures needed to correct and prevent identified quality problems[7]. This can include making planned process and quality changes, and keeping evidence of their implementation. Documentation, as part of implementation, may include new or updated implementation plans, change management records, Standard Operating Procedures, specifications, and training plans, etc.[8].

*21 CFR 820.100(a)(6)*

The CAPA dissemination phase accounted for 0.2% of the violations. This section requires a company to disseminate information relating to quality problems or non-conforming products to those directly responsible for assuring the quality of such products or the prevention of such problems[7]. 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 to all parties throughout the lifespan of the CAPA[8].

*21 CFR 820.100(a)(7)*

The CAPA management review phase had no violations during the period of this study. This section requires a company to submit relevant information on identified quality problems, as well as corrective and preventive actions[7]. 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 as effectiveness metrics and outcomes[8].

**Discussion**

There are many factors that cause CAPA related issues consistently to be the most cited violation among medical device companies (*see* Figure 1). While guidance exists and the regulation clearly explains the requirements, it appears that implementation and understanding of the requirements may not exist.

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 causes or causes, and how they will implement corrective actions. What is more important, the FDA will follow up to see that the plans are effective[9].

The FDA will be looking to see how information was collected, how it was analysed, how it was used to identify what is being looked at, identifying when to investigate or not, and the types of quality problems that are being examined. The FDA will investigate whether all quality inputs that were supposed to be looked at were in fact looked at, and that all the work has been properly documented. It will also look at procedures to show there is objective evidence to demonstrate the system is working, and that the company is in fact identifying issues from a practical perspective as

well as a reactive perspective. Additionally, the Agency will be looking to verify that the company has identified the corrective actions needed[9].

The problems noted by the study are nothing new when looking at previous time periods since the implementation of the QSIT in 1999. In a study that looked at FDA warning letters from 2002 to 2007, the number one citation was violations of FDA's CAPA requirements (820.100). The most found CAPA violations were 820.100 (a)(1), 820.100(a)(2), 820.100(a)(3) and 820.100(a)(4)[10].

A study conducted in 2010 reviewed FDA warning letters issued during 2009 and found that there were more violations of 21 CFR 820.100 than any other finding[11].

Between 2013 and 2019 this pattern held similar results. The number of overall CAPA specific warning letters averaged approximately 58% of the total warning letters issued between 2013 and 2019 (*see* Figure 1).

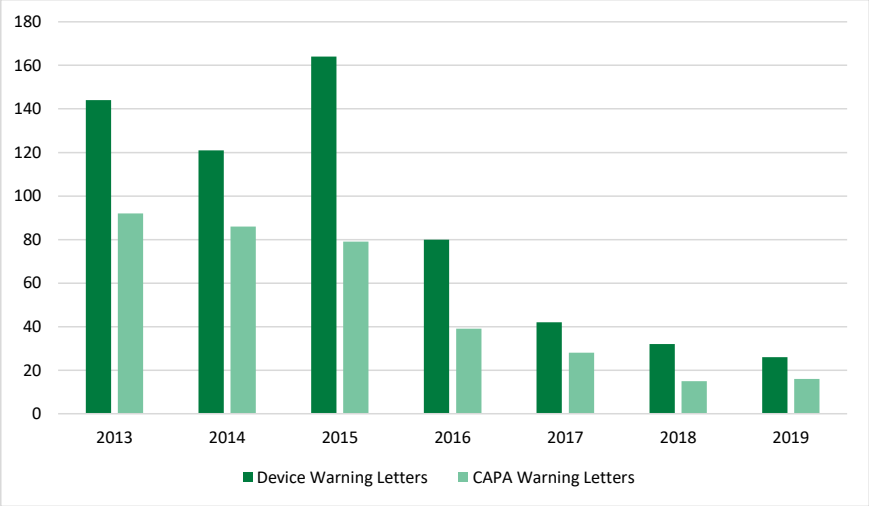


**Figure 1. 2013–2019 medical device warning letters versus CAPA warning letters**

As can be seen in Figure 1, the number of CAPA warning letters in general has been declining, especially since 2016. A possible reason for this downward trend in warning letters is that the FDA considers benefit-risk factors and a company's compliance history when determining whether to issue a warning letter. Many times, there may be an initial recommendation for a warning letter, but it ends up being converted into an untitled letter or even a regulatory meeting to take care of the problem, the general idea being that a warning letter may not be necessary[12].

The FDA has stated that between 2008 and 2017, 82% of companies corrected observed violations before their follow-up FDA inspection[reference]. The FDA also credits its Case for Quality

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**Commented [RA6R5]:** " This data indicates that the most common problems that FDA identified related to foreign medical device companies to the processes of analyzing quality data to identify quality problems [21 C.F.R. 820.100(a)(1)], investigating the cause of the quality problem [21 C.F.R. 820.100(a)(2)], identifying the appropriate corrective or preventive actions [21 C.F.R. 820.100(a)(3)], and verifying or validating the corrective or preventive actions [21 C.F.R. 820.100(a)(4)]. This suggests that the CAPA violations reflect specific examples of corrective and preventive actions reviewed during the inspection.
Less common are CAPA violations associated with documentation, such as the failure to establish and maintain CAPA procedures [21 C.F.R. 820.100(a)], document corrective and preventive actions [21 C.F.R.820.100(b)] and implement and record changes in methods and procedures and communicate those changes to the responsible personnel [21 C.F.R. 820.100(a)(5) and (6)]. This suggests that, in preparing for an FDA inspection, foreign manufacturers and auditors should consider focusing on recent critical corrective and preventive actions, instead of relying on a top-down review of the CAPA system as would be done in an ISO-style audit. This data may reflect that the FDA in looking at foreign medical companies the FDA typically notifies foreign manufacturers of an upcoming inspection approximately a month before inspection before the inspection is scheduled to start. This compares to a week's notice typically received by U.S. companies.
It is possible that with the lead-up time that foreign medical device companies had time to review and make sure that their CAPA system meet the requirements of 21 CFR 820.100 (a). The other violations indicate that a failure to look at specific examples of CAPA's which is reflected in the differing results. The results of this study looked at all CAPA violations without separation between US based and foreign medical device companies.

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Voluntary Improvement Program – which aims to evaluate product, manufacturing, and process quality at medical device companies against an industry-modified version of the Capability Maturity Model Integration framework – for a reduction in the number of warning letters[12].

While the FDA feels that warning letters are an important tool for assuring compliance, history has shown that device quality does not improve in response to issuing more warning letters. The FDA would prefer to save enforcement actions for companies with severe violations or those who fail to follow through in their corrective action plan in a timely manner[12].

Another explanation for the reduction is that between 2015 and 2019 the FDA's CDRH underwent a major reorganisation. This reorganisation was very disruptive and may have prevented warning letters being issued in a timely manner: the FDA must send out a warning letter within 120 days of a physical inspection of a manufacturer to ensure the underlying evidence is fresh[13].

While the number of warning letters has declined, the FDA is still issuing a high number of FDA Form 483 inspectional observations for CAPA related issues. Year after year, companies receive FDA Form 483s for a 'lack of or inadequate procedures' for CAPA. In fact, every year going back to 2010, the number one reason companies receive 483s is because of CAPA[14]. This serves as a reminder that the FDA still considers CAPA to be an extremely important part of every inspection and it will be examined.

## Conclusion

This study provides insight into medical device quality issues relating to CAPA through the evaluation of warning letters issued by the FDA. The results of this study indicate that despite the QSIT being in existence for over 23 years and numerous articles citing violations of 21 CFR 820.100, there continues to be significant inadequacies in how medical device companies use the CAPA system.

Approximately 72% of violations were for failure to comply with 21 CFR 820.100(a) on establishing and maintaining CAPA procedures, and these accounted for the majority of the violations observed in the warning letters. Since the CAPA system is inspected as part of all routine medical device inspections, this area receives the highest level of scrutiny by the FDA. Understanding the CAPA system and requirements outlined in the QSIT and how CAPA findings are integrated into the overall quality system is essential for device companies. Several theories abound about what causes the CAPA system to be an issue: not thoroughly understanding what a CAPA is, not recognising when a CAPA is needed, and not using the CAPA process correctly. Also, many companies do not allocate the necessary resources to administer their CAPA properly.

CAPA is a risk-based process which requires detailed and regular oversight, and there are several subparts of 21 CFR 820.100 that must be followed. To an FDA inspector, CAPA is seen as the

determining factor of the overall health of a company's quality system. Failure to recognise this could place the medical device company's whole operation under scrutiny.

This article's holistic snapshot of the period 2013 to 2019 provides insight into each of the subparts of 21 CFR 820.100 and a better understanding of where violations are commonly found in each subpart of the regulation. It also clarifies the FDA expectations for each section.

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