

**FAILING TO ESTABLISH AND MAINTAIN CAPA SYSTEMS?
YOUR COMPANY COULD BE AT RISK.**



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According to cGMP 21CFR 820.100 guidelines, “each manufacturer shall establish and maintain procedures for implementing CAPA. The procedures shall include requirements for 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.”

The pharmaceutical industry has managed its business in much the same way for decades, focusing most of their resources on the next blockbuster drug. With changes in regulations, declines in drug approvals and a shift towards developing high value biologics, today's manufacturers must begin to shift their focus and address current processes, practices and systems, and take a hard line on improving their overall quality and compliance efforts.

With more than 50 percent of Form 483 observations and warning letters citing Corrective Action/ Preventative Action deficiencies, this paper presents a practical and compliance-focused approach to root cause and corrective actions that will help transform your CAPA efforts into effective, efficient and sustainable quality systems.

At the Root of the Problem

When quality issues arise, investigating and troubleshooting these issues to determine a root cause is very important. If an investigation fails to determine the correct root cause of an issue, the issue is likely to recur, causing extensive downtime, poor customer satisfaction and potential loss of profits. For this reason, pharmaceutical companies must have a CAPA system within their Quality Management System (QMS) that provides a documented systematic approach to correcting, eliminating or preventing problems. Many regulatory agencies — such as the U.S. Food and Drug Administration and International Organization for Standardization — recognize that the effectiveness of a QMS is determined by how it is maintained. Therefore, these regulatory agencies require companies to have an effective CAPA system in place:

- **The International Conference on Harmonization Q10 (ICH Q10)**, also called the Pharmaceutical Quality System, is a guideline written by pharmaceutical industry authorities from regulatory authorities in the United States, Japan and Europe that have set the guidelines for the harmonization of the interpretation and application of technical guidelines and requirements for pharmaceutical products. ICH Q10 includes CAPA guidelines to assist companies with managing their corrective and preventative actions throughout a product's lifecycle (i.e., pharmaceutical development to product discontinuation).
- **The International Organization for Standardization (ISO)** is an international standard-setting body comprised of representatives from various national standards organizations. The organization is a non-government entity that sets worldwide industry standards. The ISO has a QMS guideline, ISO 9000, that includes sections on corrective action and process improvement. The guideline requires that companies have a CAPA system to identify and eliminate the root cause of a problem, be able to verify and execute action plans, have an effectiveness check system to measure the outcome of those actions, and a method improvement plan to prevent recurrence of the problem.
- **The United States Food & Drug Administration (FDA)** is an agency within the Department of Health and Human Services that is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, food supply, cosmetics, products that emit radiation, and tobacco products. The FDA typically inspects pharmaceutical manufacturing sites every two years. During a systems-based inspection, the FDA takes a hard approach and focuses extensively on CAPA systems. When the FDA finds failures in a CAPA system, an FDA Form 483 is issued at the conclusion of the inspection that lists all of the observations found by the inspector. The FDA district then evaluates the observations. If any of the observations are found to be of major concern, a warning letter will be issued. The FDA defines a warning letter as *“a correspondence that notifies regulated industry about violations that FDA has documented during its inspections or investigations. Typically, a warning letter notifies a responsible individual or firm that the Agency considers one or more products, practices, processes, or other activities to be in violation of the Federal Food, Drug, and Cosmetic Act (the Act), its implementing regulations and other federal statutes. Warning Letters should only be issued for violations of regulatory significance, i.e., those that may actually lead to an enforcement action if the documented violations are not promptly and adequately corrected.”* In the details of recent warning letters posted on the FDA website, it is apparent that maintaining CAPA systems is a major problem for many companies. Some common CAPA system violations described in many warning letters are not having established procedures for implementing CAPAs, having no true root cause analysis and poor documentation of CAPA actions.

In a warning letter dated June 21, 2010, the FDA stated, *“Failure to establish and maintain procedures for implementing corrective and preventive action (CAPA) as required by 21 CFR § 820.100(a)...your written Corrective and Preventive Action procedure fails to require identifying and documenting data sources and their data elements, both internal and external to your firm, in order to perform measurements and statistical techniques for the analysis of nonconformity or a potential nonconformity that may require an investigation (identifying the root cause).”*

Three Critical Elements of a Successful CAPA System

To ensure regulatory compliance, organizational effectiveness and operational efficiencies, a manufacturer's CAPA system must address areas of nonconformance and strategies to stop issues from recurring.

I. Developing a CAPA System

One requirement of a pharmaceutical quality system is the development of a CAPA system. As a regulatory requirement, the CAPA process must consist of the following key elements:

- Having documented procedures in place to define how an organization will track the records
- Performing an investigation to determine the root cause once a nonconformance has been identified
- Identifying the corrective and/or preventative actions after the root cause has been determined
- Having an established and approved action plan
- Implementing the action plan
- Having actions that support continuous improvement within the CAPA
- Having mechanisms in place to allow monitoring and analyzing of all CAPAs
- Completing all documentation and proper notifications
- Evaluating the effectiveness of the actions performed after implementation

These steps are vital for a CAPA system to be successful. The content of the CAPA should address the nonconformity; the actions must be documented and recorded; and the actions should be monitored and tracked for common root causes. The goal of the CAPA system is to show continuous improvement within the defined processes that govern the operations of an organization.

II. Monitoring and Analysis

To assure that the CAPA system is compliant and performing appropriately, the CAPA system must have a monitoring process. To effectively monitor the process, one must select appropriate measurements to show that the corrective action always addresses the root cause of the problem.

One way to assure that the established CAPAs are appropriate is to develop Key Performance Indicators (KPIs). KPIs will alert management of the effectiveness of the CAPAs and also determine if additional actions are needed. The running of KPIs against the data may be a continuous or periodic process depending on the source/availability of the data. The overall monitoring process should be routinely reviewed to assure continued suitability.

There are several tools that can be used for the measurement and analysis of the data against established parameters. The analysis will allow a manufacturer to identify nonconformity (or potential nonconformity), and identify areas that may need further investigation. In this way, the manufacturer is able to fully establish a preventative action process, allowing them to address a potential problem before impacting the product. The analysis can be performed using several methods, such as analytical tools, a team of experts or process owners.

The use of statistical tools will help the manufacturer to identify any sources of variation, determine if the CAPA has truly remedied the problem, and potentially assist in the decision-making process.

III. Continuous Improvement

The purpose of making continuous improvements to a CAPA process is to eliminate or mitigate nonconformity or the potential of nonconformity. There have been many observations issued by regulatory agencies to manufacturers that state there is a failure to establish a verification process to show the adequacy of the established CAPAs. Therefore, to establish CAPAs that will address nonconformity, a strong investigation process must be established, which includes a strong root cause analysis of the problem.

A. Root Cause Analysis

Once a nonconformity is identified, the investigation must start out by defining the problem statement. The problem statement should specify the machine, product or process in question and it should describe the exact nature of the problem. The next step is to conduct the investigation, which begins with understanding the problem data. The most efficient way to arrive at the correct root cause

Five areas that an inspector will review:

1. Procedure defining your CAPA System
2. Product trends and supporting data
3. Source of the CAPA (i.e., investigation)
4. Effectiveness of the CAPA
5. Actions that were implemented

is to ask the right questions. This will require the use of probing and clarifying questions not intended to assign blame to one particular person. These probing questions should be used to gather data and an understanding of the event in order to drill down to the root cause. Therefore, closed-ended questions (i.e., those answered with a simple “yes” or “no”) should not be used. Open-ended questions should be asked, giving the opportunity for someone to explain and elaborate on the events that occurred. The questions should focus on the five Ws:

WHO? WHAT (HOW MUCH)? WHEN? WHERE? WHY?

As part of the investigation it may be necessary to review all of the information provided, determine whether the issue is a systemic or non-systemic problem, gather additional information, interview appropriate parties, review documents and review the plant or area where the event occurred. It will also need to be determined whether there is a trend of this event occurring or if this is the first time that this event has been observed. Once the root cause has been determined, the CAPAs can be defined and implemented.

B. Identify and Verify Actions – CAPA Action Plan

After completion of the root cause analysis, a CAPA action plan should be developed to correct the situation and prevent recurrence. Creation of the action plan should be done by a group of subject matter experts from each area that will be impacted by the changes. The action plan must be well-documented and include the following information:

Task List	Develop a detailed list of all tasks required to correct the situation and prevent a recurrence.
Prioritization	Arrange the tasks in order of importance and in the chronological order in which they should be completed.
Task Assignment	Form a project team; document and communicate which tasks will be performed by specific team members.
Timeline	Outline the amount of time it will take to complete each task.
Goal	Document the expected outcome after completion of the action plan.
Training	Include training requirements for personnel affected by changes.
Tracking	Include a list of tracking tools to be used for monitoring.

After the CAPA plans have been identified and verified by the group, they must be approved by management before implementation.

C. Implementing the CAPA Action Plan

Once the CAPA action plan has been approved by management, the action items can be implemented. The actions should be completed as documented. Any large actions that have been identified should be broken down into smaller, more manageable steps. All actions and observations should be thoroughly documented. The progress of the CAPA action plan should be monitored and modified when necessary. If any modifications from the original CAPA action plan are needed, the changes must be approved before implementation and documented in the final report. After implementation, an evaluation of the impact of the actions should be assessed.

D. CAPA Effectiveness

A major part of the implementation of the CAPA action plan, as described in the previous section, is gauging the effectiveness of the CAPA. As part of CAPA system effectiveness, checks need to be developed that allow one to validate the CAPA(s). The manufacturer should have a method of gathering data over time related to the CAPA(s) to determine if the CAPA(s) is truly effective. It may be found that a specific CAPA did not fix the problem. The CAPA will need to be evaluated to determine the necessary changes and assure that there were no adverse effects as a result of the change.

The manufacturer should determine how long it will monitor its CAPA, since some actions will only require a brief monitoring and others may require an extended monitoring process. The data can then be evaluated using the appropriate statistical tools. If a new CAPA or a change to the CAPA

Common Pitfalls and Challenges

- Inability to link related problems
- Inconsistent investigation process
- Confusion over the difference between Corrective Action and Preventative Action
- Time-consuming approval process
- Changes to the action plan mid-stream
- No means to generate metrics

is implemented, then the manufacturer will need to confirm that the new CAPA has solved the problem.

E. Management Review

In the end, the responsibility of assuring an effective quality system falls to senior management. Part of the quality system is the review of an effective CAPA program. This review process can be set up in many ways — it can be a monthly management review session or a series of reviews at several levels of management. There needs to be a strong communication and escalation process to ensure that quality issues are being seen by senior management. By setting up a strong management review process, a continuous improvement environment is advocated within the company.

The parts of the quality system that should be included in the management review are:

1. Complaint, deviation, CAPA and change control processes
2. Audit system, both internal and external audits
3. Regulatory inspections and customer audits
4. Product process performance, as well as quality of product

There are additional systems that should be reviewed, but the review should establish which part of the quality system needs the most attention. Along with this review process, KPIs can be established to ease the review and identify problem areas. With each management review, resulting actions must be completed in order to address quality issues.

Glossary of Terms

When developing a Corrective and Preventative Action System, there are key terms that are defined by ISO, Code of Federal Regulations, ICH and other regulatory bodies. The following terms are frequently used when developing and maintaining a CAPA system:

Quality System	The organization structure, responsibilities, procedures, processes and resources for implementing quality management.
Quality Audit	The process of systematic examination of a quality system carried out by an internal or external quality auditor or an audit team.
Corrective Action	A change implemented to address a weakness identified in a management system; an action to eliminate the cause of a detected nonconformity or other undesirable situation.
Preventive Action	A change implemented to address a weakness in a management system that is not yet responsible for causing a nonconforming product or service; an action to eliminate the cause of a potential nonconformity or other undesirable situation.
Root Cause	The initiating source for a causal chain which leads to an outcome or effect of interest.
Continuous Improvement	Recurring activity to increase the ability to fulfill requirements.
CAPA Effectiveness	The evaluation of the executed actions taken within a corrective or preventative action.
Nonconformance	The nonfulfillment of a requirement.
Procedure	A documented description of the operations to be performed, the precautions to be taken, and measures to be applied directly or indirectly.
Key Performance Indicators (KPIs)	Quantifiable measurements, agreed to beforehand, that reflect the critical success factors of an organization.

Last year, the dominant problem areas documented on Form FDA 483 were Investigations, which accounted for 27% of the observations. The next most problematic areas were Equipment/Facilities/Operations at 11% and Validation at 10%.

Conclusion

With a proper CAPA system in place, companies can focus on the few nonconformances that may arise — instead of being overwhelmed by unforeseen issues that may come out of investigations, internal and customer audits, regulatory inspections, QMS reviews, complaints and recalls.

There are also many reasons to support making a CAPA system a priority, especially when it comes to effectively managing FDA audits, which often start with an evaluation of the company's overall operation and can influence the tone and direction of the audit.

And, having a well-thought-out CAPA system as part of a QMS may result in successful audits, fewer investigations, less product loss, better customer satisfaction, and an increase in overall operational efficiencies.

Using a systematic approach to correcting and preventing the issues, measuring the outcome and continuously monitoring the system can ensure that a company is compliant, effective and efficient — with fewer issues and greater returns in today's competitive market.

Sources

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To establish CAPAs that will address nonconformity, a strong investigation process must be established, which includes a strong root cause analysis of the problem.



About CIS

Compliance Implementation Services (CIS) is a consulting firm specializing in compliance strategies for the pharmaceutical industry, from Global Clinical Research and Development, through Manufacturing, U.S. Commercial Compliance, and Government Programs. Founded in 2004, we provide our clients with a deep understanding of industry laws and regulations, innovative and practical applications, and custom solutions to establish a “Culture of Compliance” that is both meaningful and sustainable.

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