CAPA,
Customer Satisfaction, and the FDA

MERIT SOLUTIONS

Content

1. Introduction

Companies in the life sciences industry would prefer to focus on their successes. No one wants to worry about a product that might fail or attract customer complaints.
Unfortunately, complaints and problems with products happen. And if we don't take care of them properly and in a timely fashion, we will suffer the consequences, delivered by the FDA and the courts.
Customer complaints can be avoided when life science firms ensure that their processes and procedures produce the highest quality products. This guide shares how to build a culture of quality, what to look for in an outsourcing partner, maintaining a CAPA system, and dealing with the FDA. Following these steps should reduce nonconformance to procedure, improve the quality of your output, and eliminate customer complaints.

2. Warning Letters and CAPA

Executives in life sciences organizations that make regulated products have a legal duty to ensure that their company implements whatever measures are necessary to comply with the complex and stringent requirements of the FDA (and other worldwide health organizations) – and they can be held personally liable for failing to conform with regulations.
Two events that keep these executives up at night are upcoming audits and the issuance of 483 observations and warning letter citations.
Warning letters are considered informal and advisory, but the FDA will only issue them when the agency considers a problem to be of significance. The warning letter serves as a signal of the FDA's intention to pursue legal action if the company does not take corrective action, but the FDA usually only uses warning letters when it has a reasonable expectation that the company will take the necessary corrective actions. Otherwise, the use of warning letters serves as the first step in legal action and as a notification to senior management that the company is under scrutiny.
An FDA audit is often the trigger for a warning letter, but other events may also prompt the agency to issue a warning. For example, the agency issues warning letters in any situations where it believes that the company is in violation of the law. This may include advertising or marketing claims, incidences of misbranding, mislabeling or counterfeiting, or suspicion that the company is promoting products for uncertified usage.
The FDA usually doesn't issue warning letters if it believes that the firm's corrective action system is adequate and would soon result in the resolution of the problem. They may undertake an additional or follow up audit to verify that the CAPA system meets its requirements and that the company has implemented the recommended actions. This makes an effective CAPA system extremely important, for the following three reasons:

1. CAPA can identify quality problems early in the cycle before problems become severe.
2. CAPA can provide reassurance to regulatory agencies that the company is capable of resolving issues.
3. CAPA can convince the FDA (or other regulatory bodies) that identified problems have been resolved.

The FDA publishes a list of all warning letters it issues, so a warning letter can harm the company's brand reputation as well as open it up to legal sanctions, fines, and even imprisonment of key personnel. There are well-defined procedures for clearing warning letters, which the company must follow in order to have the warning letter closed. The FDA may require additional audits before it agrees to close a warning letter.
A CAPA system is essential for any regulated company, but it can be especially useful in dealing with resolving warnings and other regulatory sanctions because it provides audit trails of the steps the company has undertaken to resolve the problem.

3. All Roads Lead to CAPA

CAPA is considered by many to be the holy grail of the quality management system. It can be the convergence of change control, continuous improvement, complaint management and tracking and trending. Executing a CAPA system and repeating it is critical to survival. It is a reflection of a company's ability to react both proactively and reactively to address issues.

3.1 Navigating Without a Map

An undefined or inconsistently employed CAPA system will result in a compliance gap that will be revealed during an inspection. Most CAPA 483s are due to either an inadequate process or inconsistent process adherence. More specifically:

- Failing to define escalation to CAPA
- Inadequate process or failing to follow the process
- Insufficient documentation
- Inadequately assessing effectiveness

3.2 Finding the Way

Establishing a CAPA system should start with understanding how the standards define CAPA. A correction refers to an action to eliminate a detected nonconformity. Corrective Action is an action to eliminate the cause of a detected nonconformity in order to prevent recurrence. And a preventative action is an action to eliminate the cause of a potential nonconformity or other undesirable situation in order to prevent occurrence.
Some issues may actually result in a combination of actions but only corrective action and preventative action require an effectivity check. In this stage you must provide evidence that the issue was actually fixed and that the fix did not affect anything else.
One of the first steps must be to provide guidance on which nonconformances should be escalated to CAPA. In some cases, a company's procedures may not define this and therefore the decision is left to the discretion of the user. This leads to too many issues finding their way into the CAPA system or too few never getting there at all. Too much traffic in the CAPA system bogs down the process and prevents issues that truly warrant a CAPA from expedient implementation.
A risk based approach can assist in removing subjectivity around the CAPA decision. Those issues that adversely impact the patient, the operator, or the employee should be escalated to CAPA. The company may also consider the frequency of the issue in the overall assessment.

Once you have decided to initiate CAPA, the record should contain the following basic elements:

- Clearly define the action taken. This should link back to the original problem statement noted in the nonconformance or the investigation. This helps to prevent scope creep. It can be very tempting to think that you can boil the ocean.
- The action should be aligned with the root cause. If you don't address the correct issue, the CAPA may ultimately be ineffective.
- Create a plan and establish responsible parties to meet expected milestones. Gain agreement up front from all parties involved.
- Define the plan for the effectiveness check.

It should also be noted to periodically update the record to ensure adherence to the timeline and to assist in overcoming obstacles. You must consider the risk to product that any delays may cause. The FDA will be concerned if you take a long time to fix an issue. It implies that you are continuing to make and distribute potentially bad product. In the meantime, you must demonstrate that the issue was contained.

3.3 A Good GPS

Although some companies still have paper or rudimentary electronic systems, a dedicated quality event management system is the best bet. These tools provide defined templates to document records and provide easy access for data analysis and tracking and trending. Whatever system is utilized, clear procedures, properly trained staff and a helpful tool will assist in arriving at the destination of compliance and safe and effective products.

4. The Care and Feeding of a CAPA System

A robust CAPA system is sustained by subsystems that provide feedback into CAPA. There should be appropriate mechanisms in place to facilitate this flow of data. This is not a static system but rather a continuous loop. The risk becomes apparent when the CAPA loop remains unclosed. The result may be a CAPA that is opened for years or a CAPA that really didn't fix the problem. The goal of continuing to collect data is to reduce the number of issues encountered as well as the severity of those that do occur.

After a CAPA has been implemented, it is important to monitor data to determine if the issue has been resolved. Any question of the CAPA's effectiveness must be answered with data - so it is important to facilitate a feedback mechanism to gather and analyze incoming information. Effectiveness monitoring is an area where some companies falter. Once a CAPA is deemed effective, the record is closed.

In addition to the initial effectiveness determination, the FDA expects that there is a process where the changes or the issue is continually monitored and that data continues to be fed back to determine if the issue has resurfaced or if the fix may have caused another issue to occur.

An inspector may ask to see how data is captured, trended, and assessed. Ideally, a free flowing system leads to early detection of an issue and drives preventative actions. The company can address a problem before a nonconformity occurs or before it reaches the customer's hands.

4.1 Proactive vs. Reactive

Perhaps out of denial or out of a lack of understanding, companies ignore the positive potential of data and starve the CAPA system. They take the view, "If we ignore it maybe it will go away." These firms will continue to behave reactively. A well fed CAPA system is healthy. It identifies and fixes issues early.

4.2 What Goes in Must Come Out

The sustenance for the CAPA system may vary. The data should be appropriate to the category of the product, the complexity of the product etc. Be sure to sort through the data to differentiate that which is valuable and that which is not. The filters to sort the data are typically based on risk such as intended use, patient results or treatment decisions. The choices should be based on standardized criteria to evaluate the criticality of the issue. Don't overlook the importance of appropriate training for the individuals reviewing the data and making these decisions.

4.3 Is It CAPA or Not?

The established risk categories will guide companies to create levels or a threshold that when reached, action is taken. If every issue required a CAPA, nothing would get done. Frequency, severity of harm and trends all enter into the CAPA decision. These decisions should be clearly documented either procedurally or in the individual record (nonconformance, complaint etc.).

4.4 Management's Menu

Executive management needs to review the health of the CAPA system. They should know the:

- Number of CAPA opened
- CAPA aging
- Due date extensions
- CAPA effectiveness
- Risk levels
- Trends
- Preventative vs. corrective actions

These criteria can provide the managers with actionable information to allocate the appropriate resources. Managers can also provide a bird's eye perspective across departments or manufacturing sites not apparent to someone entrenched in a particular product area.
It is management's responsibility to interpret and ensure that a well fed CAPA system is neither starved of value added data nor gorged on unnecessary noise.

5. Being Reasonable: A Guide to Preventing FDA Obstruction

In 2013, the FDA issued a draft guidance document (Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection) regarding the types of actions that would be considered to obstruct an FDA inspection and potentially lead to a supposition of adulteration. In October 2014, the final guidance was issued. The document attempts to define what behaviors are considered an intentional delay or refusal. The FDA has the authority to enter any facility under the jurisdiction of the FD&C Act at reasonable times and conduct inspections.

5.1 Delays of an Inspection

Some inspections are pre-scheduled. The investigator will contact the facility and negotiate an acceptable date. Reasonable considerations can include holidays, weather or other local issues beyond the company's control. An example might be if the local utility company is digging up the road outside the facility or working on power lines, it may not be the best time for an inspection.
The FDA will level a charge of adulteration if the facility:

- fails to agree to a date and can't provide a reasonable explanation
- changes the agreed upon date without providing a reasonable explanation
- is unresponsive to communications

5.2 Delays during an Inspection

This is probably the more common behavior. Any activity that impedes the investigator while at the site from conducting the investigation can be categorized as a delay. Minor delays are expected and will probably be accepted with a reasonable explanation. An example might be that an SME is out of town but you are trying to reach them by phone. A particular service may be outsourced and you are arranging a conference with the appropriate individuals may be another acceptable consideration.
A citation may result if:

- A facility does not allow access to a particular area and cannot agree on a time when that can occur.
- A facility leaves an investigator in a room without anything to review beyond a reasonable period of time.

In the previous example, there is really nothing stopping the investigator from leaving the room and wandering around the facility unescorted.

5.3 Delay in Providing Records

Records are the holy grail of your processes. The FDA recognizes reasonable explanations such as record storage is off site or a particular request is large and will need additional time to compile. There are off site record vendors that provide 24 hour delivery. Reviewing records electronically is another option to fulfill the request. An unacceptable delay is determined when a facility fails to provide the records in a reasonable timeframe.

5.4 Limiting Inspections

This is a broad category of behaviors that may include

- Limiting access to a particular building or area
- Limiting photography
- Limiting access to an employee to conduct an interview
- Limiting access to specific records
- Preventing copies of records or taking samples

5.5 Refusal of Entry or Denial of Inspection

This can include hindering the FDA from conducting or completing an investigation. This may be through direct actions or passive behavior with the intent to avoid, mislead, deceive or impede the investigation.
This may include:

- Refusing entry without a reasonable explanation
- Repeated rejections of attempts to schedule the investigation
- Unresponsive to communications
- Falsely reporting the facilities use

The FDA expects cooperation from each facility to attain the objectives of the inspection. Every company should be inspection ready at all times. Understand what is required during an inspection. Maintain inspection procedures and train staff on how to handle an inspection. When the facility is in tip top shape and the documents are in order, you'll be primed for when the doorbell rings.

6.When Obstructing the FDA Becomes Criminal

When the FDA warns of further enforcement, it is not just an attempt to intimidate. There are teeth behind this procedure and companies need to recognize that. Ignoring or excessively delaying a response will not make it go away; the ramifications will only worsen.

6.1 The Consent Decree

One of the FDA's tools is the consent decree. It is essentially a court order that describes the conditions under which manufacturing can occur under close scrutiny by a third party and or the FDA. Depending upon the agreement, the company may be required to discontinue production. In other cases once manufactured, the product must be reviewed by a third party. The cost for this outside review is paid by the company.
Consent decrees cover a broad range of issues that represent a pattern of non-compliance to the regulations. There may be repeated 483s during inspections or warning letters with unsatisfactory responses. This is important as a company may be communicating with the FDA during this time; however, the plan to correct the deficiencies is not acceptable. It may take several years to satisfy the agreement. During this time, corrections must be executed to bring the processes back into compliance. The company can make changes to their quality system in order to avoid litigation. Timelines are critical as missing a commitment may lead to fines.

The fines, the dollars necessary to bring a facility up to standards, the loss of revenue if product cannot be sold and any third party resources can cause the total cost to skyrocket. When a company does not respond or comply with the FDA, the agency then can request the Justice Department to file criminal charges. A company is notified of the charges either through a subpoena to provide records or other information or when federal agents execute a search warrant at offices or other company facilities.

6.2 The Tipping Point

There is a term for the consent decree called "sign or sue." It means that either you agree to hand over control of some of your operations or you enter into litigation. The investigation looks for evidence of fraud, concealment of information, obstruction, repeat violations, the severity of the violations and risk to public safety. Prosecutors will review this evidence and determine whether to proceed with further litigation.

6.3 Enforcement Journey

The noncompliance road does not unfold overnight, but it may be inherent in the corporate culture and increasing pressure to meet the bottom line. Companies directing fewer resources into manufacturing improvements and quality systems may be the cause. Prosecution hopes to send a message to any of the FDA regulated industries that they may be next. The FDA offers companies opportunities to correct violations. Litigation typically occurs only in the most severe cases.

7. Building a Culture of Quality

When questioned if their company has a focus on quality, most managers and employees will say yes. This might be because at a minimum, it is the right thing to say. They may also believe that since they have some procedures or a quality policy that this suffices and that quality practices will just fall in to line. Under further scrutiny, however the differences between perception and reality become apparent.
The view from higher levels in the company may be that the firm has a well disseminated quality culture. But as you travel down the organizational chart, the response may not be so positive. A culture of quality is a full time commitment to quality. It is not just referencing standards in a few SOPs. Everyone should understand who the customer is and what he or she expects.

7.1 Critical Elements

Leadership needs to articulate expectations by setting goals and measuring performance. Without clear leadership, you will see different perspectives on quality practices and performance as you move throughout the organization. Management must consistently endorse:

- A quality vision statement that is well articulated and communicated. Employees must feel that the vision is supported by management.
- A quality program driven by customer needs, engaging customers in determining customer satisfaction.
- Methods of identifying and addressing problems. Individuals and departments need to be proactive.

7.2 Putting the Pieces Together

Companies with a successful quality culture have these traits in common:

- Vision, which has been described as a business case for quality. It should be clear and imperative.
- Values, which are the inherent standards that drive decision making.
- Leadership committed to the values and vision.
- Building consensus from the big-picture managers to the line operators.
- Measurable metrics develop data driven decisions.

These companies set expectations so everyone is accountable, quality is everyone's responsibility, and everyone is a stakeholder. Training focuses on the importance of quality. These firms have programs to reward behaviors that drive quality and empower everyone.

Risk taking must strike a balance with innovation. The fear of failure shouldn't be an impediment to trying new things. Focusing on quality allows for risk taking in a measured way. Continuous improvement holistically ensures that a positive impact in one area doesn't cause a negative impact in another.

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7.4 Customer Focus

Customer focus is at the forefront of quality initiatives. It is understood that this drives profitability and competitive advantage. Successful companies recognize:

- Customer focus is a continual process and reacts as their needs change.
- Gather feedback through multiple methods.
- Deliver what the customer wants.
- Provide an outstanding customer experience.
- It is important to invest in technology that improves the customer experience.

7.5 Reasons for Concern

Although companies may believe that they are focused on quality, there are some signs that would indicate that this may be wishful thinking or blatant denial, such as:

- Lack of processes for gathering customer feedback.
- Lack of processes for continuous improvement.
- Lack of quality metrics.
- Poorly communicated vision.
- Lack of training on quality.
- Presence of recalls or a high number of customer complaints.

Operating in a culture of quality is more than words spoken during a mandatory meeting or captured in a slide deck. Although well intended, it will probably not achieve the goals. Leaders must be examples of creating and cultivating a quality culture. People must be motivated from within and demonstrate an inherent desire to do the right thing all the time.

8. Customers are Complaining - Make Sure You Are Listening

One of the most common reasons for FDA warning letters is deficiencies in complaint handling. They typically fall into the following areas:

- Inadequate procedures or failing to follow procedures to collect, document and interpret complaints
- Inadequate timeliness of closure
- Inadequate connection of complaints to reportable requirements

A complaint is any customer dissatisfaction with quality or performance and may include packaging or labeling.

Given that broad definition, it may be a difficult task to have processes in place to handle complaints as it becomes hard to sort through and give each an appropriate evaluation and to further escalate and take action on the serious ones. Products that pose a significant risk to the user are more regulated and it is expected that they are captured and investigated efficiently.

8.1 Complaints are Not Created Equal

A medical device can be anything from a toothbrush to an implantable. The FDA utilizes a three tier classification that defines the expected level of control to establish safety and efficacy.

- Class I has the highest risk and is defined as situation in which there is a reasonable probability that the use of or exposure to a violative product will cause serious adverse health consequences or death.
- Class II is not expected to cause injury but may impact patient care.
- Class III is defined as a situation in which use of or exposure to a violative product is not likely to cause adverse health consequences.

A manufacturer needs to consider the risk of the product when evaluating the complaint. There may be reportable requirements depending on the classification of the product. Companies should have a designated complaint

handling unit and provide appropriate training in interpreting the risk of the issue as well as instruction on reportable criteria.

8.2 Capture and Document

Complaints may be obtained through a number of portals: call centers, e-mail, service calls, etc. These contacts need to be documented in a complaint file. Sufficient information needs to be collected in order to correctly classify the complaint and to begin the investigation. Some companies have a checklist or a script for individuals receiving complaints to follow to aid in complete data capture. They also have return kits to streamline the return of the product if needed. Incomplete information of the failure makes defining risk and root cause difficult. On top of this, once the manufacturer has been made aware of the issue, if the event is reportable, the regulatory clock starts ticking. The investigation needs to begin as soon as possible to facilitate timely resolution and provide feedback to the customer.

8.3 Investigations and CAPA

Where appropriate, the manufacturer needs to document investigation activities. Not every complaint requires an investigation; however, procedures should provide guidance and rationale for initiating investigations. Timeliness remains important, especially for the higher risk products. The closure time is directly related to the amount of time spent on the investigation and CAPA. The expectation is that appropriate resources are applied and that the issue does not languish in an ongoing investigation. An inadequate or inconclusive investigation impacts CAPA. It is necessary to understand root cause to effectively interact with the CAPA system.

8.4 Continuous Improvement

Customer dissatisfaction is certainly undesirable. Complaint resolution can be laborious. With correct categorization and the appropriate allocation of resources, timely resolution and regulatory compliance can be realized, though.
Effective complaint management is critical to resolving issues in a timely manner and provides feedback to the Quality Management System for continuous improvement and satisfied customers.

9. Choosing a Contract Manufacturer: It's all in the Family

With increased scrutiny on the supply chain and rising complexities, finding a dependable manufacturing partner is critical. Outsourcing to a contract manufacturer may seem like an easy thing to do if your company does not have the expertise, equipment or capacity to manufacture a product. You turn to a distant family member to fill in the gaps and move on to something else. However, if not sufficiently evaluated or controlled, the solution becomes the crazy aunt you wish would go away. Ultimately, the sponsor company is accountable to ensure that the contract manufacturer is compliant with cGMP and applicable Quality System Regulations.

9.1 Know What to Look For

How do you know that contract manufacturer has the capability and the quality system to meet the demands of a regulated industry? There are some steps to sufficiently evaluate their capabilities prior to selection.

A review of other products or components they have manufactured can be used in part to determine their level of expertise. Keep in mind that it is possible for a CMO to not be specific about their capabilities in order to get the contract. They may believe that they can deal with issues as they arise. As the sponsor, you must have a supplier selection and auditing process. This will facilitate the decision to go with that manufacturer.

Compare their quality system to your own. The success of the relationship may be based in part on how well the two quality systems align. Check their certifications. Contract manufacturers may be audited by the FDA based on the risk of the device. Product defects originating from the CMO is an obvious indicator of quality problems. Look for past 483s or warning letters. In the future, it is possible for both the contract manufacturer and the sponsor to receive a warning letter if the issues found are significant.

Review the change control and CAPA processes to ensure that they meet the intent of the regulations. Qualified operators should have documented ongoing training. The appropriate equipment must be present to meet your needs and that it is validated and maintained. They should have internal auditing procedures and a schedule of audits.

9.2 Careful Communication

Communicating changes is a two-way street. Agreeing on the impact of a change may be challenging if each company has a differing interpretation. The sponsor and the contract manufacturer must work closely together to ensure a successful design transfer. Clear documentation and communication will lay the path for positive outcomes.

A written agreement is necessary to ensure that communications occur. Contracts should express a synergy of quality expectations. The following provisions in the contractor/quality agreement are recommended:

Clearly state the specific responsibilities.

- Provide copies of certifications and registrations.
- Evidence of a robust quality system.
- Communicate any 483 or warning letters.
- Submit timely notification in writing of any changes to raw materials, components, equipment or specifications.
- Communicate of nonconformances that may have impact to product.
- Show evidence of validation for equipment, software and methods.
- Have clear specifications and acceptance criteria.
- Agree to periodically audit the facility.

Building and maintaining the relationship is critical and continues throughout the life of the product. Outsourced service providers should have a place at the table. For an ongoing successful relationship, you must think of them as an extension of yourself and your team.

10. Conclusion

A customer complaint doesn't have to spiral out of control, leading to an FDA audit, fines, penalties, and the closure of your business.

Companies don't have to let things get that far, though. By integrating quality controls into the very fabric of their day-to-day operations, their employees will reduce the errors they make and produce a better product. Creating and maintaining a CAPA system will also help diminish mistakes.

While it isn't easy to develop a culture of quality and implement a CAPA system, it is vital to the success of your company. Your customers trust you to sell them a product free of defects and danger. The FDA's role is to ensure you don't destroy that trust. Choose suppliers and other partners who share that mindset, maintain the highest levels of quality controls, and your customers will be satisfied.

Life Sciences organizations have to account for a lot of moving parts when trying to ensure they have a future-proof infrastructure. Maintaining and simplifying regulatory compliance, enhancing operations both digitally and by weeding out inefficiencies, and taking the steps necessary for growth – these are all steps which require a highly coordinated approach.

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