CAPA plan: The right approach

Freyr recently released a white paper which demonstrates that CAPA should not only correct and prevent the quality issues, but also proactively apply the approaches practiced to prospective areas where the issues might ensue

INVESTIGATING QUALITY related issues and tracking them to closure is one of the most critical activities in quality management system (QMS). The increased importance of risk-based approaches is leading regulators to look for a well-defined process in investigating and identifying the root cause and method of implementation of the Corrective and Preventive Action (CAPA) plan. The crucial questions, most frequently asked by auditors during a CAPA review, include:

- Have the correct root causes been identified?
- Have the CAPAs been tracked and closed on time?
- Have the proposed CAPAs been reviewed for quality?
- Have all the proposed actions been implemented?
- Have the CAPAs been effective in preventing recurrence of the same problem?

Most pharma companies view CAPA as an activity intended to address identified quality issues but fail to take a holistic approach to address them. This is evident from the warning letters published by Regulatory Agencies. Such a partial approach to CAPA results not just in rework, but also loss of time and revenue.

Successful CAPA management requires addressing quality issues efficiently and effectively. CAPA should not only correct and prevent the quality issues, but also proactively apply the approaches practiced to prospective areas where the issues might ensue. By evaluating industry trends and pain points, going forward in this article will look into insights that help achieve regulatory compliance.

Overview

The most common method used for fixing any quality issue is the Corrective and Preventive Action (CAPA) plan. Following is a trend analysis of all non-conformities published by the Food and Drug Administration (FDA) in their 483s, which clearly outlines the impact of CAPA process on Regulatory agencies.

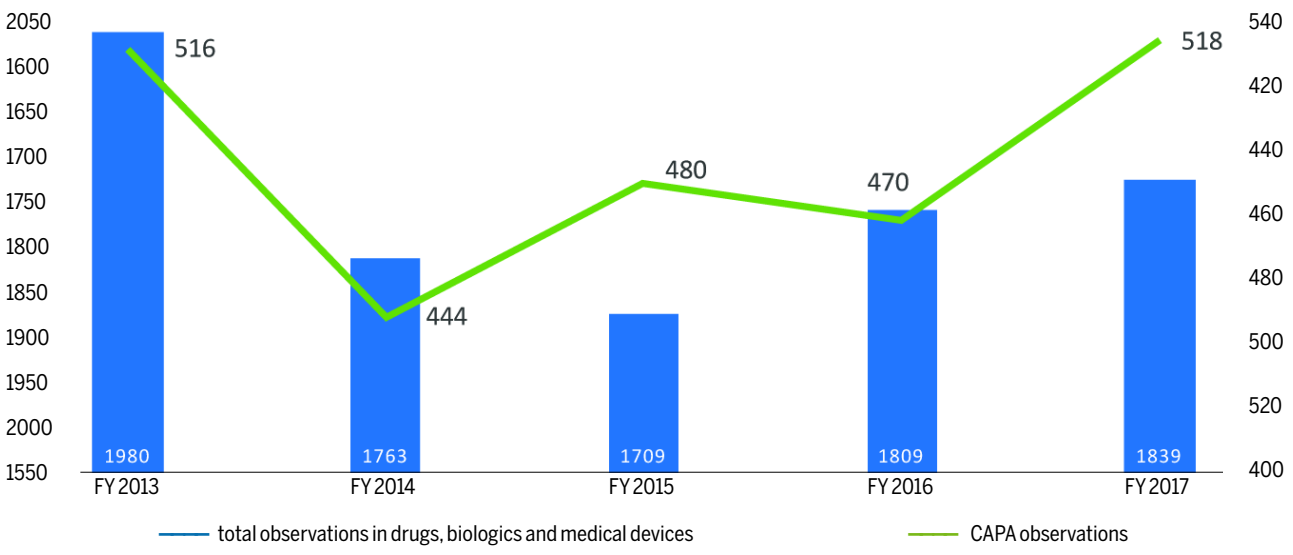
The analysis clearly shows that almost 25-29 per cent of non-conformities are CAPA related, which translates into more than ¼ of all the FDA's observations. Thus, establishing a robust CAPA system warrants that the number of non-conformances is reduced by a quarter.

To understand if the existent CAPA system / process for companies is fool-proof and can withstand stringent audits, an analysis was conducted on the areas where issues related to CAPA are identified by the auditors. All CAPA related observations were broadly classified into the following categories:

- Inadequate procedures for CAPA
- Inadequate CAPA documentation
- Incorrect / inadequate / non-compliant CAPA

On detailed analysis of non-conformances, it was inferred that all the three categories: inadequate procedures, inadequate documentation and inadequate controls were interlinked. Inadequate measures were taken when there were inadequate processes. Inadequate documentation was ob-

Type of CAPA observations	Frequency of observations				
	Fiscal Year 2017	Fiscal Year 2016	Fiscal Year 2015	Fiscal Year 2014	Fiscal Year 2013
Inadequate Procedures	400	344	378	362	380
Inadequate Documentation	115	99	97	101	133
Inadequate Controls / Actions	3	1	5	7	3
Total CAPA Related Observations	518	444	480	470	516
Total Observations in FY	1839	1709	1809	1763	1980
Percentage of Observations on CAPA	28.17	25.98	26.53	26.66	26.06



served when there were no adequate measures to record them, and hence no artefact to submit.

Inadequate procedures

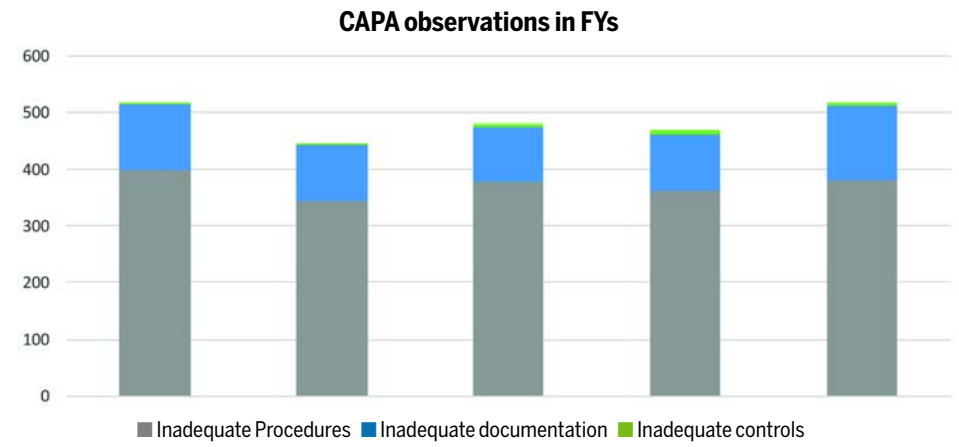
Understanding and implementation of current Good Manufacturing Practice (cGMP) includes updating the procedures in line with current Regulatory requirements. Legacy procedures do not include mitigations for known risks in the process and risks due to CFT interactions. Additionally, lack of proper training and procedure implementation is a widespread problem in the industry.

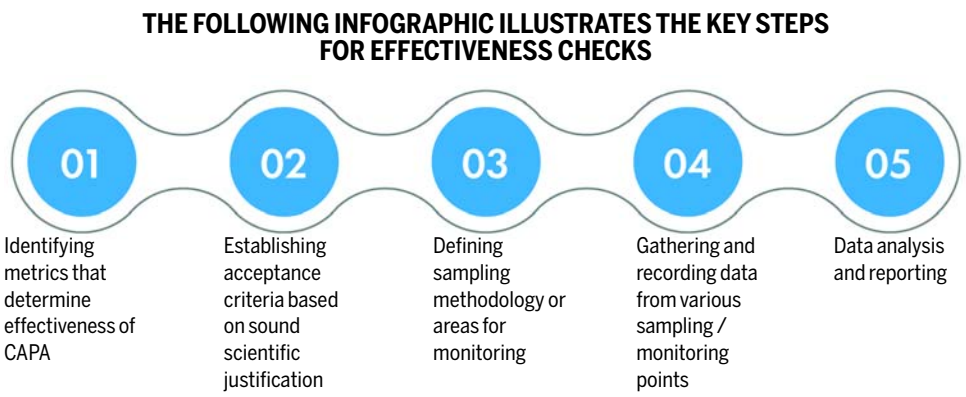
Effectiveness checks

The cases discussed above reiterate the untapped stepwise-verifying effectiveness of CAPA. If the measures taken on the CAPA are not effective, the process requires re-opening of CAPA, re-investigation, identification of root cause, and if required, a new CAPA plan.

Freyr's 40+ years of combined compliance resource experience has been providing effective and efficient solutions to its customers on a wide range of CAPAs. Implementing simple changes in a procedure and re-training of personnel is a key as a CAPA action requires a straightforward approach to measure effectiveness. Some CAPAs propose more extensive changes, such as changes in testing process, change in vendors, changes in infrastructure layout, implementing a new system, to name a few. Effectiveness checks for such CAPAs require niche experience since this involves analysis and monitoring of adequate sample data. Quantitative approaches are recommended over qualitative ones to measure effectiveness checks since the former not only provide proof of effectiveness, but also offer opportunities for improvement.

Effectiveness checks not only help us to determine if the CAPA is constructive, but also helps us to determine if it is feasible to implement. In the process of establishing a concrete process which leaves no scope for errors, organisations fail to consider the challenges that the ground level staff encounter. This makes the process difficult to adhere to, which in turn leads to other non-conformities and errors despite proper training. Assessing risks to the process with appropriate stakeholders will identify various hurdles in implementation and thus prevent such issues.





Conclusion

To resolve institutional complications, every organisation should conduct an effective investigation, identify root cause(s), and implement timely and practicable corrective and preventive action(s) (CAPAs). An effective CAPA process should aim to promote critical thinking within the organisation at all the levels. The process must provide a common model and risk-based framework within the organisation, which allows investigators to master the process quickly and easily. This would anchor common logic behind investigations and bring unity to problem solving. The goal is to implement a reusable, standardised, and complete process that can avoid similar CAPAs.

CASE STUDY - I

Incorrect / Inadequate / Non-compliant CAPA

A warning letter issued to a drug manufacturer in the year 2017, stated, "during inspection of your analytical lab, the firm invalidated 101 out of 139 (about 72 percent) initial, out-of-specification (OOS) assay results for six-month stability assay, without conducting proper investigation. The initial failing result was invalidated without sufficient investigation, following which re-testing was performed and then reported as being within the limits.

The firm failed to determine the assignable cause and did not take appropriate CAPA to ensure that the significant "analytical bias," to which the initial analysis failure was attributed to, did not impact other analyses performed in the laboratory.

The firm's investigation assumed that there was analytical bias in the laboratory but failed to determine how this error in analysis could be eliminated or mitigated in the future. The firm's response was termed inadequate by the FDA since they failed to implement CAPAs to mitigate the issue that was attributed to their process.

However, the firm initiated an investigation into the OOS identified and a CAPA was assigned for the same. Despite the firm's efforts, this was considered inadequate by the authorities.

Authorities expect the CAPA plan for a given issue to be effective in preventing its recurrence. This, unfortunately, did not happen in the above-mentioned case, resulting in its relapse.

To address this non-conformity, it is crucial to identify exactly where the process was ineffective. The non-conformity may be due to any one of the following reasons:

1. The root cause identified after investigation was inappropriate: The OOS identified could have been the result of some other issue such as complications in manufacturing, faulty storage conditions for the sample etc., which led to its 138-times recurrence.

2. The CAPA plan was not suitable: The root cause identified, i.e., analytical bias, may have been due to a variety of reasons such as material, machine, calibrations, persons, methods and so on. The cause identified is far from the bull's eye and identifying a CAPA for an unknown factor with vague causes is difficult to achieve. Additionally, it was not evident if the CAPA plan covered all the areas of analytical bias and efficiently rectified them.

3. The proposed CAPA plan was not validated for its effectiveness: Effectiveness checks need to be periodically conducted during the CAPA process. Not performing these effectiveness checks to determine if the identified plan has resolved the issue, results in repetition.

In the above case in point, the issue has occurred over a span of six-months. Some issues may even occur over a longer duration. Monitoring every issue that occurs in a facility and trending them on periodic basis is beneficial to the process. Additionally, validating the CAPA for its effectiveness closes the loop between issue identification and remediation, while also providing proof for the same. Thus, leading to a closed loop CAPA process.

CASE STUDY - II

In a warning letter issued to a Medical Device company, the FDA stated, "Failure to establish and maintain procedures for implementing corrective and preventive action, as required by 21 CFR 820.100(a).

For instance,

Your firm's CAPA control procedure, does not include requirements for:

- Analysing all sources of quality data to identify existing and potential causes of non-conforming product, or other quality problems
- Verifying or validating the CAPA to ensure that such action is effective and does not adversely affect the finished device
- Implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems

›

Your firm's procedures indicate that three different CAPA forms can be used:

- The CAPA and Improvement Record
- Customer Complaint Record
- CAPA and Non-conformance Record

During the investigator's review of the CAPA files, four CAPAs were found to be documented on forms called "Quality Problem Records", that was not mentioned in your firm's procedure. None of the four CAPA files included documentation of all corrective actions, implementation dates, or effectiveness check information as per your CAPA procedures. Your firm stated that a retrospective analysis of all historical and open CAPAs would be performed. However, your firm did not include documentation or evidence of the correction and the corrective action."

When such non-conformities are identified, the integrity and oversight of the Quality Assurance (QA) department are questioned. In the iterated instance, the procedure does not define various triggers for a CAPA, such as internal and external audit observations, out of specifications, deviations from procedure and so on. All these are quality issues which ideally should have been included in the procedure. Adopting a risk-based approach will help in identifying more failure scenarios for CAPA initiation. When an issue or discrepancy is identified, it is difficult to identify all possible causes without usage of rational methods. Detailed investigation involving use of methods such as 5-why analysis or Ishikawa diagrams in conjunction with critical thinking methodologies such as K-T problem solving techniques help in the identification of the accurate root cause.

Once the root cause has been identified, it is imperative for the organization to correct the issue immediately to avoid having repeated issues. The correction may be technical or procedural or both, which did not occur in the above case.

Designing a standard operating procedure (SOP) that encompasses every possible error, that is easy to comprehend and practical, as well, is the first step to address the above observation. This, in turn is critical for efficient operation and seamless closure of retrospective investigation of CAPA

Inadequate documentation

Regulatory authorities emphasise on the availability of documented proof or objective evidence for any activity performed. Failure to provide the same consequently leads to non-conformities. For an inspection, manufacturers are required to present CAPA documentation that can demonstrate to the auditors that the manufacturer's QMS is efficient and effective in identifying issues quickly and can implement effective CAPAs. Any discrepancy in the documentation provided attracts unwarranted questions and mistrust from the agency.

CASE STUDY - III

In a warning letter issued, FDA states, "IM-CAPA-007 was opened in for bladder ruptures and remained open for (b)(4) days. The root causes identify (b)(4); (b)(4); and (b)(4) of the (b)(4). The corrective actions include implementing an (b)(4) and adding preventive maintenance on the (b)(4). Your effectiveness verification after three months was performed with a review of complaints which determined that the corrective actions were effective. The effective summary opened for the Intermate and Infusor bladder ruptures states that the validation document number V07-055 demonstrated that the (b)(4) of the bladders improved by (b)(4) %. Protocol document number V07-055 validated the new compounding rubber process using (b)(4) equipment with water-cooling system. A review of the documentation (protocol and records) revealed:

- The protocol specifies that the (b)(4) test is for information only and it does not specify an (b)(4) acceptance criterion for bladders
- There is no record showing 50 samples were pulled from three production lots,
- There are inconsistencies within the production lot numbers as specified in the protocol and final report"

In the illustration, the organisation did have an efficient procedure for addressing issues through CAPA. However, the organisation failed to implement and enforce the same at an operational and process level. Gaps and discrepancies in processes and documentation gave rise to irregularities in data, thus presenting difficulties in validating effectiveness.

In the above case, the firm failed to establish a sampling methodology, hence leading to inconsistencies in sampling and documenting them. Also, it failed to define the acceptance criteria based on which the process could be deemed effective.

In addition to this, there was an increased risk of receiving observations on data integrity and Attributable, Legible, Contemporaneous, Original and Accurate + (ALCOA+) practices in the organisation.

The outcomes of adequate documentation are bountiful. It not only helped us in achieving the famed '0 Observations', but also provides the management with opportunities for improvement