CAPA Management:
Challenges and some practical solutions

A KINAPSE GUIDE FOR THE LIFE SCIENCE INDUSTRY

kinapse

a SYNEOS HEALTH company

Table of content

Introduction:

Non-compliance occurs all the time across the Life science(s) regulated industry. It comes from a variety of sources, including customer complaints, annual product quality reviews or internal/external audits, and causes, including misinterpretation of instructions or poor training.

Regulatory agencies recognize this. What they look for is how an organization investigates and manages such non-compliance; the FDA specifies in 21CFR820.100 that '*(a) Each manufacturer shall establish and maintain procedures for implementing corrective and preventive action*.' and '*(b) All activities … and their results, shall be documented*.' Consequently, CAPA Management is a critical activity for life sciences business success.

CAPA Management is not, however, new. It has existed and evolved over many years. Quality professionals in this industry know that the only way to manage non-compliance is by having in place an effective **closed-loop CAPA Management system.** Such a system, if set up and used appropriately, ensures that any non-compliance can be addressed quickly and efficiently, with action plans implemented that will both redress and prevent re-occurrence. Not only is this type of system required but Kinapse believes that, done well, it will save an organization valuable time and money while empowering employees to become proactive in problem solving.

Who would benefit from reading this White Paper?

- Quality Control/Quality Assurance team – Who understand the value of effective CAPA management but struggle to get the business to engage
- Individuals who are assigned as a lead in their function, with responsibility for performing non-compliance investigations in a pharmaceutical, clinical, manufacturing, biologics and medical device environment

Why is CAPA Management not embraced by the business?

In established Life science operations addressing non-compliance, is all too often seen as an unwelcome drain on time, effort and resources teams just cannot spare. In addition, the formalised nature of CAPA Management can feel like overkill when the cause appears to the experienced team as perfectly obvious. In this case a CAPA is seen only as a task to be completed and documented to create metrics and show 'compliance' to the regulations – with no benefit to their work - and so it should be kept at a bare minimum at all times.

Life science organizations are under tremendous pressure to keep pace with new and revised regulations. Changes are driven by external factors, e.g. greater data protection rights (GDPR), calls for greater transparency (CTD), or can be triggered by the industry itself.

Inspection observations that reflect ineffective CAPA Management systems are noted but can sometimes be viewed by the business as an issue for the Quality or Compliance function, as the CAPA Management system is owned and managed by them. Funding for such a 'support' system and commitment to making full use of it is lacking with the result that many companies still do not have a robust CAPA Management system in place. This is supported by data in Figures 1 and 2.

The concept that robust CAPA Management is a fundamental tool in creating a system that is 'self-correcting' which, in turn, supports improved operations and keeps quality at an optimum level, is not well understood. Clearly, for many, the business case and benefits of a CAPA Management system and the Quality team's role in facilitating (but not owning) its throughputs have yet to be made.

Figures 1 and 2 demonstrate that during domestic and internal Medical Device inspections performed by the FDA in 2017, it continues to find observations related to 'ineffective' CAPA Management systems.

This paper will focus on the essentials of a CAPA Management system, and discuss some of the challenges observed across life science organizations related to this topic, and practical solutions from Kinapse experts.

"Life science organizations are under tremendous pressure to keep pace with new and revised regulations."

FY2017 Domestic & Foreign FDA Form 483 Inspectional Observations

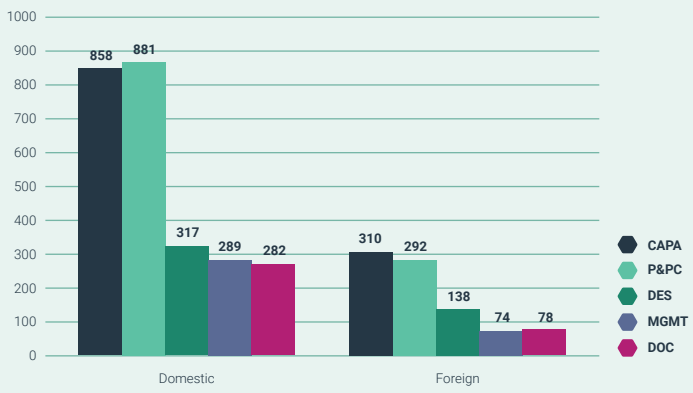

Figure 1.

FY2017FDA Form 483 Observations

QS Subsystem	# of Observations	Percentage
P&PC	1173	34%
CAPA	1168	33%
DES	455	13%
MGMT	363	10%
DOC	360	10%
Total	**3519**	**100%**

Figure 2.

Foot note 1: https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHTransparency/UCM597261.pdf

What does an effective CAPA Management process look like?

As discussed in the introduction, regulatory agencies continue to see observations related to not having a robust CAPA Management system in place. For that reason, the FDA published guidance2 on what constitutes a CAPA Management.

Foot note 2: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-guides/corrective-and-preventive-actions-capa

The Kinapse CAPA Management approach aligns with this guidance. Developed by our recognized subject matter experts and incorporating industry best practices realized along the way, it aims to simplify the steps for stakeholders with little experience in CAPA Management and so empower them to work effectively alongside their Quality Assurance teams.

The Kinapse CAPA Management process is broken down into five (5) steps, as shown in Figure 3.

Thirty days is a commonly applied timeline for steps 1 to 3.

Figure 3: The Kinapse CAPA Management Process

Step 1: ***Identification:*** Identify the problem/non-compliance, write a clear problem statement and make an initial impact assessment. The problem statement is about the current observable condition, not about a perceived solution, cause, or what one may want to have happen. In order to write a good problem statement ask and/or answer these questions:

- What happened?
- What should have happened?
- When did it happen?
- Where did happen?
- Who identified it? Who was involved?

Make an initial assessment of the impact based on the information known at this time.

Step 2: ***Investigation:*** Before an investigation report can be written, identify the cause of the problem/non-compliance. Take care to focus on the problem itself and not the symptom. Focusing on the symptom leads to temporarily masking the problem, can make the problem worse or allow the problem to reoccur. To avoid treating the symptom, follow these steps.

- Begin the investigation as soon as possible so that the events are fresh in everyone's mind and evidence is available
- Observe the scene and review the relevant documentation
- Interview the individuals that were involved
- Gather all the facts. Facts may come in the following forms: (i.e. diagrams, batch records, cleaning and equipment logs, deviations, change controls, etc.)

Once the information has been gathered, sort through the facts, and select the most appropriate Root Cause Analysis (RCA) tool for the non-compliance in question. Table 1 shows several of the most commonly used. Some RCA tools are directly geared toward identifying true root causes; others are more general problem-solving techniques; and others simply offer support for the core activity of root cause analysis. Each has value. Kinapse provides RCA workshops to show when to use each of these tools.

Table 1: Root Cause Analysis Tools

RCA Tool	What is it?
5 Whys	The purpose of the 5 Whys is to look into the levels of causes and/or identify the root cause. To do this, one must repeatedly ask "Why?" when a cause has been identified, thus progressing through the levels toward the root cause.
Fishbone Diagram	Fishbone or Ishikawa diagram is also known as the Cause and Effect method. It is a visual tool used to logically organize possible cause(s) for a specific problem or effect by graphically displaying them in increasing detail. Root causes are arranged according to their level of importance or detail. This will assist with assigning priority when implementing corrective actions. Related cause(s) can be usefully arranged into 6 major categories; Machine, Method, Measure, Materials, Man and Environment.
Fault Tree Analysis	It is an approach that assumes failure of the functionality of a product or process. The results are represented pictorially in the form of a tree of fault modes.
Pareto Technique	It is a statistical method which employs the 80-20 rule, which states that about 80% of the problems or effects are produced by about 20% of the causes.
Brainstorming	The basic premise of brainstorming is that a group of people collectively try to find a solution which is more productive, imaginative and innovative than the one single solution.

Once the investigation RCA has been performed, develop the Correction, the Corrective and Preventive (CAPA) and the Effectiveness Check (EC) plan(s). The plans will have to correct the non-compliance, eliminate it from recurrence, and eliminate the cause of a potential non-compliance, if applicable. The plan(s) should enable the following:

To complete the Investigation Step 2, draft the Investigational Report. It should include the below information:

- Event summary
- Description of the deviation/non-conformance
- Materials/lots affected and rationale, if applicable
- Trend Analysis or Historical Review to confirm if a similar deviation/ non-conformance has occurred previously
- CAPA and Effectiveness Check Plans
- Root cause investigation
- Impact accessment

Step 3: ***Review and Approve:*** All parties impacted by the non-compliance and/or responsible for the required CAPA/EC actions review and approve the Investigational Report, RCA, CAPA(s), and EC(s). Consensus is enough- formal documented approval is not needed. Product impact, if deemed applicable, is determined based on all the information gathered to this point.

Step 4: ***CAPA implementation:*** This step will check whether the correct steps were taken to rectify the non-compliance. Confirmation of completeness supports this and provides documentation to prove to regulatory authorities that the CAPA was implemented. Implementing the CAPAs may sometimes identify/introduce new issues/challenges where the investigation was not completed appropriately. In this case, restart at step 2 – Investigation.

Step 5: ***Verification:*** Close the loop by performing an EC for each CAPA implemented. Closing the loop between identifying the problem and completing the actions to address that problem helps prevent loose ends, which could negate earlier good remediation actions. Close loop follow-through can safeguard the benefits of the CAPA team's efforts.

The following tools and principles can
be used to help make effectiveness checks successful:

- Provide trend analysis data will showif another CA should be established or if the fix was successful
- Perform periodic checks
- Conduct a surprise audit to check that compliance is being maintained
- Conduct sampling, for example as it relates to laboratory Quality Control testing
- Establish a due date that allows enough time for the CA to work while maintaining a sense of urgency to ensure the problem is fixed

If a CAPA is deemed effective, then no additional steps need to be taken. If CAPA is deemed not effective, then a complete re-investigation needs to be performed to identify whether the true root cause was determined during the initial investigation. Again, the process will need to restart at step 2 – Investigation.

Correction should:

1. Be S.M.A.R.T. – (Specific, Measureable, Achievable, Relevant, Time-bound)
2. Address the current problem
3. Prevent it from becoming a bigger problem
4. Be tracked
5. Not have a long due date

CAPA should:

1. Be S.M.A.R.T.
2. Address root cause(s)
3. Prevent recurrence of the problem
4. Consider business applications
5. Include instructions
6. Include name of action owners
7. Be tracked
8. Consider Future implications

EC should:

1. Be S.M.A.R.T
2. Be related to RC and CAPA
3. Indicate duration – Start and stop time
4. Contain success criteria
5. Describe the evidence required to verify CAPA was successful
6. Include EC owner name

CAPA Management challenges and some practical solutions

Much attention is given to CAPA Management tools, but none of them will be effective if they are not properly implemented. On the flip side, it could be that Life science organizations implement everything correctly, but there are other factors that are not taken into consideration. In Kinapse's experience, the below list includes the most common issues with CAPA Management, along with our insights/solutions/and or other resources that can help.

1 Getting the right team to determine the RCA

Ideally a Quality Assurance person, along with the relevant stakeholders who are related to the non-compliance, should be part of the investigation team. This is because most non-compliance involves multiple departments across an organization. If all the key members are not included it could lead to missing potential root causes. Having all functions affected represented on a team, will help to collect data, conduct the investigation fully and impartially, and make it more likely that all potential factors are included in the analysis. Furthermore, this wider participation encourages acceptance of the CAPA(s) and recognition of the value.

Kinapse Insight/Solution:

Not all non-compliance will require an investigation team. This will most likely occur when the problem is more complex. If complex non-compliance should occur then a CAPA Review Board meeting should take place prior to any investigation team being established.

2 Writing a good problem statement

The key to begin an investigation of a non-compliance is to first fully understand what actually happened; what constitutes the real problem. If the problem/non-compliance is not understood then it cannot be eliminated.

Kinapse Insight/Solution:

A good problem statement must include the failure and the identification. The following questions need to be asked for failure: What happened? What should have happened? Where did it happen? When did it happen? The following questions need to be asked for identification: Who identified the problem? When was it identified? How was it identified? Once these questions are all answered, the problem statement can be drafted.

3 Lack of knowledge regarding RCA tools

Some Life science organizations, for various reasons, still do not have a reliable set of tools and methods for carrying out an investigation. Others have a lack of understanding of when and how to use the root cause analysis tools.

Kinapse Insight/Solution:

Kinapse offers a CAPA Workshop that educates the attendees about the different types of RCA tools and when to apply them, and improve their skill set. Furthermore, a breakout session allows the attendees to apply and practice the tools on a scenario where a non-compliance has occurred.

4 Listing 'Human error' or 'procedures not followed' as the root cause

For many of the non-compliances observed within an organization – listing human error or procedures not followed as a 'root cause' is quite common. Conducting a training is often the CAPA. These root causes are often abused, because the RCA tools have not been used properly and hence the real issue is not determined. In most of the cases, this is often the symptom. The investigator of the non-compliance needs to do a deeper dive, and determine why the errors were made. It might be that there is a bigger or non-obvious problem within the quality management system.

Kinapse Insight/Solution:

Kinapse can assist by taking a look at your organizations' CAPA and Quality Management systems and executing a gap analysis. Additionally, prepare metrics to capture the common and recurring issues and collect data that can be analysed. Once the analysis has been performed, Kinapse will offer solutions based on what is determined to be the overall problem.

5 Meeting timelines

Though guidance(s) and regulation do not particularly mention any timelines, it is not uncommon for senior management – keen to show that actions have been taken, and mark it as 'closed' in management review meetings – puts pressure on the investigation team to resolve a non-compliance as early as possible.

Kinapse Insight/Solution:

In Kinapse's view an organization needs to establish timelines upfront. Typically, this is 30 calendar or business days. Remember is that the investigation should be completed with quality in mind and not merely meeting a deadline. Often hard to do with competing priorities and deadlines. If this is the case, Kinapse can provide experts who specialize in conducting investigation, RCA, developing CAPA and EC plans, investigation writing, and monitoring closure of CAPA and ECs.

6 All 'non-compliances' are claimed to be an isolated event

During investigation, a historical review can confirm whether the non-compliance has occurred previously.

Kinapse Insight/Solution:

The importance of a historical review is essential because, it is a check and balance of the CAPA Management system. If it is not confirmed then it shows that the investigation team has done their due diligence, and that it is indeed an 'isolated' event. However, if it is confirmed then a deeper analysis needs to be performed as this may be evidence of a bigger issue within your CAPA Management system. It is an indicating factor that previous non-compliances either were not investigated or were improperly corrected. Kinapse suggests that a fixed timeframe should be established for historical reviews and included within CAPA Management procedures. Furthermore, the process of how to perform a historical review should also be proceduralized.

7 Not all Root causes are acknowledged/corrected

It is imperative that when multiple root causes are identified, each has a corresponding CA or PA. Often a team creates only one CA, thinking it will resolve all the root causes. Leaving a root cause unattended or addressing it indirectly as part of a group often makes it more likely that the issue will repeat, rendering the whole process worthless.

Kinapse Insight/Solution:

Kinapse recommends that CAs be created for each root cause so nothing gets missed. Link each CAPA with each root cause e.g. by assigning linked numbers/references. This approach will make it easier when it comes time to review the CA, and then later match the EC.

Conclusion:

Kinapse believes that by applying the CAPA Management insights and solutions its people have gained over decades of experience and outlined here in this paper, a Quality Assurance team can:

- develop skills to facilitate operational teams in meeting their responsibilities without taking over or becoming the unwelcome face of the problem
- instil clarity to hone agreed actions to the appropriate and realistic
- drive the process with timely, specific reminders
- ensure that non-compliances are resolved in the same manner
- promote continuous improvement
- help the organization meet regulatory requirements and business needs and in so doing
- encourage the business to positively value CAPA management

If you think our Subject Matter Experts may be of help to your organization in developing actionable recommendations and innovative solutions, please contact Renata Skros at: **Renata.Skros@kinapse.com.**

Authors:

Renata Skros

Kinapse Quality and Compliance Manager

Renata has been working in the Pharmaceutical Industry since 2000, with experience ranging in Quality Control Microbiology, Quality Systems, and Regulatory Affairs. She has an extensive knowledge of both Commercial (sterile and non-sterile) and Research & Development. She specializes in GMP, GLP, Deviation writing, review and processing, CAPA and Effectiveness Check Management, Complaints processing and review, Annual Product Review processing/review, SOP Document Management, Initiation/Review of Change Controls & Planned Deviations, and lastly Performing Gap Analysis on Quality Control and Quality Systems procedures. She has overseen a number of continuous improvements projects such as; Assisting in the Development of Laboratory Training Documentation Management/Retention, Development of Archival procedures for Logbooks, Introduction of Forms into the Document Management System, and was in involved in the Enhancement as it relates to the Quality of Writing of Deviations. She greatly enjoys investigating Major and Critical Events, and seeing that the associated corrective and preventive actions were effective.

Asha Francis

Kinapse Quality and Compliance Consultant

Asha has been working in the clinical research industry since 2000. Her expertise lies in GCP compliance. She started her career as a Quality supervisor in a government research centre which conducted WHO trials. She then moved on to work in a leading CRO which provided end to end services for clinical trials where she was responsible in defining the QA program for clients, measuring compliance, and led key successful assignments related to clinical trial internal audit, external audit, vendor audit, trial site management and also advised on GCP compliance issues. She was resident expert involved in writing client-specific SOPs, review and revision of existing ScPs, performing gap analysis of QMS as well as training on SOP's. Currently at Kinapse as a subject matter expert she is exclusively focussed on CAPA Management for her clients.