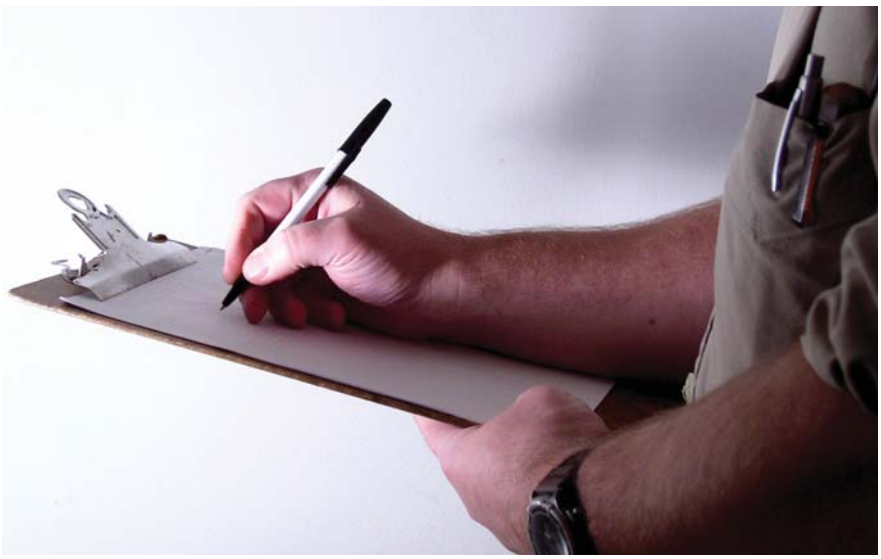
Navigating CAPA

by Paula J. Shadle

Pharmaceutical GMPs have a long-standing set of requirements regarding the pursuit of quality improvement. For example, both the European GMPs and 21 CFR 210–211 require that failures be investigated and actions be taken to improve quality (**1**, **2**). Similarly, US medical device regulation 21 CFR 820 coined the term CAPA for corrective and preventive actions and stated clear requirements that companies perform and document CAPA promptly (**3**).

Meanwhile, investigators at the US Food and Drug Administration have experimented with several paradigms for conducting inspections: Team Biologics, QSIT inspections, and so-called "traditional" inspections. Feedback provided at conferences, in warning letters, and through 483 findings indicate that the FDA has shown an increasing interest in quality-systems approaches and CAPA during inspections. In 2003, the FDA announced its intent to pursue risk-based assessments to prioritize inspections, evaluate data, and determine follow-ups. Regulators have also indicated that they expect each company to perform its own risk assessments and use them to justify and schedule CAPA. Taken together, risk-based GMPs represent attempts to go beyond a check-box mentality to protect the public health from real and potential safety risks.



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Where Then Are the Difficulties?

Most lie in the gray area: issues important enough to keep on the to-do list but that consistently rank below other clearly critical items. Judgment and experiences vary, so no one can be confident that his or her own risk assessment will be accepted by all auditors. After acknowledging this difficulty, companies need to set their own approaches and be prepared to justify and defend their decisions at any time. Investigators need training to ensure that they can negotiate differing approaches. A review by central FDA scientists of all warning letters in draft is an excellent step in aiding this process and assuring consistency.

PRACTICAL PROBLEMS

A company that sets up a robust system to generate CAPA actions without performing capacity analysis may quickly find itself with a large backlog of open actions generated from many activities, usually governed by different procedures. Some companies end up with several independent CAPA tracking systems; others use a single system that collects actions from independent and diverse sources such as deviations, internal

audits, inspections, licensing commitments, failure investigations, complaints and recalls, supplier audits, and trending of analytical data. It is important to design a system upfront so it assures transparency, allows the quality unit to track commitments and progress, and documents interim activities taken on open actions that will demonstrate due diligence and appropriate risk assessment and prioritization.

In the past, many companies used manual logbook-based systems to

FDA Warning Letter and 483 Findings

FDA Violations	Concern
Company failed to follow SOP requiring audits of all class three suppliers each year	Not following procedures
Company's testing program for incoming raw materials is inadequate: Nitrogen with product contact was accepted on certificate of analysis inspection.	Lack of identity testing may create a safety issue
Many deficiencies remained uncorrected since the last inspection (five months before)	Lack of CAPA
Inadequate system to deal with vial defects found during sealing operation: Type of defect is not documented; evaluation of type and number of defects is not performed to identify probable causes; product impact is not assessed; CAPA are not implemented.	Pattern of deficiencies in follow up
Company fails to test raw material for organic volatile impurities (OVI) even though C of A states, "OVIs may be present but will meet specifications if tested"	Quality of raw material may be unsuitable
Raw data are being changed with no justification	Data integrity is suspect
Errors in calculating results not detected during second check	Reviews may be inadequate
Supplier kept at "reduced testing" status despite three lot rejections of raw material	Company is not responding to negative data; systems do not detect change
No documentation that critical reagents were qualified before their use in QC testing	Pattern indicates that QC testing may be unreliable
No assurance that specifications are current and accurate	System not being maintained
Calculation errors were missed during the second review	Reviews may be inadequate
SOP does not address repeat testing when samples do not meet assay acceptance criteria	Potential lack of objectivity in QC; selective testing based only on results
No method transfer study was performed when analytical method was transferred from another site	QC testing may not be reliable or in a state of control; lack of validation
The company did not follow its inspection SOP, in that it did not go to an increased inspection of stoppers following a lot rejection for major defects, and stopper defects identified by inspectors were overruled by supervisors without a documented explanation	Company is not responding to negative data; reduced inspection unlikely to detect defects; no assurance that defects are being found by the process used.
Test results were invalidated due to insufficient analyst training without adequate justification	QC may not be objective; not finding the root cause
No procedures for review and approval of QC data and errors found	Reviews are inadequate
Lack of detection of pattern of failures: 250 "isolated" incidences of the same test failure	Lack of trending; inadequate oversight; failure to detect patterns
Events that are reportable are not submitted to the FDA in a timely matter	Lack of responsiveness and oversight
Full investigation was not conducted into water that exceeded microbial action limit, no corrective and preventive actions were initiated	Lack of CAPA
All actions needed to correct/prevent recurrence of nonconforming product have not been identified; not all reports of quality data have been analyzed to identify existing and potential causes of nonconforming products	Lack of CAPA
No indication senior management assures that all CAPA actions are implemented in a timely way	Lack of in-depth CAPA
14% of all product nonconformances are attributed to analyst/human error	Root cause not found
Three lots failing glycerin testing were not investigated, nor were root causes found	Investigation

Table 1: Most common QC deficiencies

Problem	Solution
Inadequate procedures	Strong development effort to define critical parameters
Incomplete records	Use QA documentation systems; decide whether QA documentation specialists should support QC; design forms for use and review; self audits
Inadequate OOS investigations	Improve training and oversight; follow up to confirm that root causes were found; monitor with metrics
Inadequate instrument qualification	QC cannot be prioritized below manufacturing for validation support; change control, validation master plan, and schedules are required
Sample handling and results release	Assure that controls over sample storage and preparation are adequate; train analysts to inspect samples; traceability
Inadequate training	Use metrics to evaluate the effectiveness of SOP revision training, general lab training, technique proficiency, and general GMP training.

Case Study: False Positives in the Microbiology Lab

Results on samples run as negative controls to check for contamination control indicated that a QC lab had an intermittent problem. Analysts were retrained several times; environmental monitoring results appeared to be good; cleaning frequency and stringency were increased, and several technique changes were made, all without effect. Meanwhile, tests of aseptic techniques such as media fills were highly successful. Finally, manufacturing and QC staff together walked the line from sampling through laboratory testing.

Two root causes were found. First, sample collection containers required QC analysts to open them and set up the test, creating a risk of sample contamination. Second, the QC hood was in a high-traffic laboratory area near an entrance, and disturbances in air flows were common. The test was moved to second shift, and ultimately the hood was relocated; sampling was done using new closed devices designed to facilitate testing set-up. Not only did the negative controls show improvement (no positives detected), but the bioburden estimates in process samples decreased significantly. Clearly, analyst technique was not the root cause, and no amount of retraining could have solved the problem.

track CAPAs. Such systems suffer from some common deficiencies.

Lack of Transparency: People are not made aware of their tasks, the due dates, and how they are doing against target dates. Some CAPA items remain buried, for example, in filed audit reports and do not get entered into the tracking system.

Inadequate Design: The system does not properly assign actions to the right person, and it cannot reassign items to someone else when needed. Laborious searching is required, even in a computerized system, to get a global view or generate metrics.

Lack of Visibility: Upper management often has no information about how many CAPAs are open, their importance, or which areas are falling behind. That means management cannot do a risk assessment that could help boost critical CAPA actions to a higher priority level. Unfortunately, such deficiencies may be perceived as a lack of buy-in to real quality and can cost the company greatly in its relationship with inspectors and investigators.

Lack of Classification: A CAPA system that does not permit sorting of critical items from noncritical ones may result in a first-in–first-out approach to closing actions that is inappropriate given the varying risks. A mature CAPA system may contain many low-priority, low-impact items, especially preventive actions, for which extensions can be — and are — justified. In poorly designed CAPA systems, administrative resources are spent on the extension process, and the big hitter CAPAs are no more visible than the minor ones.

Lack of Resources: Studies in the automotive, healthcare, aerospace, and food industries have shown that, in the long run, spending money on prevention is less costly than spending it on remediation. A focus on short-term cost reduction will cause resources to be pulled away from longer term preventive work. Finding the best balance between long-term and short-term activities is difficult and usually requires dedicated staff. A company may experience a conflict between regulatory requirements to do effective and complete CAPA actions and the need to get product out the door. In many cases the same staff work on both activities, which might create a conflict of interest. After all, if improvement is more work for me, why wouldn't I just decide the process is good enough?

Automation is of great assistance in alleviating practical problems by increasing access and visibility, permitting classification of CAPAs, and automating reminders and metrics generation. Quality staff are freed up to work more on CAPA content issues and can quickly get management input when priorities need to change. However, automation does not assure that root causes are found in investigations, that the actions proposed are relevant and useful, or that issues will not recur. Those are content issues that require management commitment.

Content: Ensuring CAPA Are Effective

Among the concerns expressed by investigators regarding CAPA programs are the content and

scientific quality of the investigation and its follow-up. For example,

- Ensuring the investigation was adequately thorough and in-depth
- Confirming that the root cause was actually found and that the CAPAs proposed do not just address the symptoms
- Assuring that the potential effect on other systems, lots, or products is identified properly so that any actions will be global
- Balancing timeliness with completeness when they conflict
- Addressing fears that complete, honest documentation may result in worse inspection outcomes than would downplaying risks.

The "FDA Warning Letter" box lists examples of typical findings taken from warning letters to illustrate these patterns (**4**).

Thorough Investigations: To perform a thorough investigation, personnel must be trained and experienced enough in both technical and compliance issues to be able to probe, collect, and interpret data and propose hypotheses. One manager reported that using his most experienced staff resulted in the best investigations and most appropriate CAPAs, but the trade-off seemed to be that more deviations occurred when experienced people were taken off the plant floor for CAPA activities (**5**). Intensive training, including pairing up staff on investigations, can help to assure the quality of investigations and prevent generating nonvalue-added CAPAs. Ongoing training within a work unit should include summarizing investigations and their outcomes so the entire work unit benefits from lessons learned.

The most important decision related to any investigation is whether to extend it beyond the lot, test, or item that originally triggered it. If a stoppering malfunction was detected in one lot, should the investigation look at the lots stoppered before and after it? Or at all lots filled on the line? Senior input from subject matter experts and compliance expertise from QA are both required to make the decision and assure it can be justified. FDA 483s and warning letters frequently cite a failure to expand the scope of an investigation of impact, as shown in the "FDA Warning Letters" box and Table 2. When in doubt, conduct some additional evaluation such as a sampling, audit, or re-review to get data in support of your decision.

Root Causes: How do you know whether the root cause has been found in an investigation? When all the data can be explained, the fix is implemented, and follow-up shows evidence that the problem is not recurring (or recurs at a lower frequency). In other words, certainty will be established only over time. Monitoring for data trends is crucial to obtain evidence that will determine whether a problem stays solved. Any recurrences should refer back to older CAPAs, even closed ones, to indicate that relevant connections were recognized at the time. One company was cited for "250 isolated occurrences of the same problem" (**6**). Such a lack of linkage is hard to defend. For examples of investigations that found unexpected root causes, see the case study boxes.

Case Study: Analyst Errors

As part of efficiency analysis, several QC work units were asked to report metrics on the frequency of out-of-specification (OOS) results and the root causes found. One work unit reported a high rate of OOS results that were not confirmed and resulted in invalidation of test data. Because 70% of the observed OOS results were invalidated, the laboratory performed a great deal of retesting and investigation and its capacity plummeted while cycle time became unpredictable.

The table lists brief summaries of the causes ascribed to several laboratory failures. The pattern was initially missed because it did not correlate with a single analyst, a shift, a test method, or a production sample. When the work unit was compared with others in QC, the invalidation rate stood out, and the cause lists clearly indicated a single problem: failure to follow the procedures exactly. What then were the root causes? Several hypotheses were examined:

- Analysts not trained
- Procedures written poorly
- Lack of supervision
- Lack of resources causing analysts to rush.

The corrective action taken after each event — retrain the individual analyst on the specific method — clearly wasn't changing the overall metric.

Table: Reasons for Invalidation of OOS QC Results

Cause Listed	Corrective Action
Incubation done at 35 ºC instead of 37 ºC	Retrained analyst
ELISA plate stored at 4 ºC for 30 minutes before reading	Retrained analyst
Four instead of five replicates were tested	Retrained analyst
Step four performed before step three	Retrained analyst
Test method run outside of validated range	Retrained analyst and updated SOP
Over-incubated ELISA plates	Retrained analyst and reviewer
Dilution error	Retrained analyst
Expired standard was used	Retrained analyst

What did affect the OOS rate was additional training and a QA person in plant to support the supervisor, who was spread too thin in overseeing a large number of employees. Many analysts had less than six months on the job and were in various stages of training. Some attitude adjustment was needed to convince the staff that innovation was not acceptable, and group retraining was found to be more effective in changing work habits.

Preventive Actions

Corrective actions will resolve an issue as it affected a lot in question and permit disposition of that lot. Preventive actions are designed to correct potential problems (risks) identified during an investigation and reduce the probability of new risks. In most organizations,

preventive actions are negotiated between work units and QA. Discussion and questions often concern how much is enough.

For example, should the entire WFI system be serviced when one exceeded action limit is found? Or, if one analyst is caught falsifying data, what should be done with all other analysts and supervisors? The following questions can help to guide these decisions, but ultimately an organization needs to look at its patterns and the effects of potential quality problems and choose how aggressively to pursue preventive actions.

- How easily can this problem be detected, should it occur?
- Does it directly affect patient or worker safety?
- Is it likely to lead to product rejection?
- Is it leading to a reportable regulatory problem?
- How difficult and expensive is the preventive action proposed?

Any potential problem that could clearly affect safety should be subject to aggressive and in-depth action. A potential problem that cannot be detected reliably is of greater concern than one that can, because it may mean that defects can slip through QC controls. Additional procedural controls are especially helpful in such circumstances. For obvious reasons, it is advisable to act when a risk is likely to result in a problem reportable to the FDA. For example, adverse events, error and accident reports, stability failures, and the production of lots by a process not able to meet NDA or BLA specifications all have strict requirements with time limits for reporting to the FDA. Costly corrections are more than made up for when they avoid a single lot recall or withdrawal.

Prioritization by criticality will create a mixture of preventive actions that include good practices that do not appear to be urgent. Those items can be given lower priorities by assigning longer due dates; they can be grouped together for efficiency or picked up using routine maintenance systems such as periodic review of SOPs. By definition, those actions are less likely to result in critical findings if neglected. But how should you manage them?

Keeping Score

A periodic report that summarizes the on-time performance of critical, important, and minor CAPAs is helpful. Simple rules for escalation of low-priority preventive actions are also useful. For example, once a CAPA has been late three times, perhaps it automatically assumes a higher level of importance, or it automatically routes for a sanity check (does it still make sense?). The most useful activity is to group open CAPAs and look for patterns that may have been missed. Is one group overloaded with actions? A pattern of repeated items means that the priority should be increased and the investigation made broader.

A well-designed CAPA system is an essential communication tool for executive management and the quality unit to perform adequate, balanced risk assessments and be aware of quality from moment-to-moment. The more visible and up-to-date their information is, the more easily management can carry out its responsibilities. Why, then, do so many companies lack adequate CAPA systems?

Perhaps such a database is not seen as value-added because it tracks problems. Perhaps it has to do with the fear that "if I put all of the dirty laundry into my CAPA system, then I just gave the agency a road map to write a 483 violation." Such a belief can lead to off-the-record CAPA activities that make it difficult for anyone inside or outside the company to tell how resources are being used, what the priorities and driving philosophy are, and what the state of quality is. A European inspector noted at the PDA–FDA Joint Conference that he is more likely to be favorably impressed by a company that has detected and is attempting to address its issues than by one that appears to be hiding problems from itself (7). The FDA's recent statements about risk assessment suggest a similar approach. It is important for industry and regulators to have dialogue regarding important but not urgent CAPA items and the limits of acceptability. It is rather like deciding how much home insurance to buy.

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