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**Corrective Action Preventive Action (CAPA): A Risk  
Mitigating Quality System**

**Published in Pharmaceutical Engineering, Volume 28,  
Number 3, May/June 2008**



## Risk Mitigation

This article identifies ways to mitigate the risk associated with the manufacture of drug products.

# Corrective Action Preventive Action (CAPA): A Risk Mitigating Quality System

by Gamal Amer

### Introduction

As most everyone is aware by now, the FDA<sup>1</sup> issued guidance in August 2002 titled "Pharmaceutical CGMP for the 21<sup>st</sup> Century: A Risk-Based Approach; a science and risk-based approach to product quality regulation incorporating an integrated quality system approach." In order to fully appreciate the importance of the guidance, one needs to understand the following issues:

- What is risk and to whom?
- What events cause or increase the level of risk?
- How does risk manifest itself?
- How to define risk levels?

This article will attempt to answer these very specific questions before attempting to identify ways to mitigate the risk associated with the manufacture of drug products.

### What is Risk and to Whom?

The International Conference on Harmonization (ICH) defines risk in Q9<sup>2</sup> as "The combination of the probability of occurrence of harm and the severity of that harm." Thus, risk is associated with detectable harm happening to an entity, which can be measured through a probability and severity. In the drug manufacturing process, risk is associated with an event that would compromise the quality, safety, and/or efficacy of a drug. Such compromised drug product could harm patients and the public in general. In some cases, the risk could affect the personnel manufacturing the drug, such as in the case where potent compounds are being manufactured. In other cases, the harm can befall the drug manufacturing com-

pany itself such as in the case where the company is found to be non-compliant with regulatory requirements and is assessed a fine or prevented from continuing to manufacture the product. In other words, risk is the probability of an event occurring, and it will occur, which would harm the patients, public, the personnel, or the company itself, and the severity of such an event.

This article will focus on addressing the risk to the public/patient that would occur during the manufacture of a drug, basically risk associated with Good Manufacturing Practice (GMP). It is the legal as well as the moral obligation of the drug manufacturer to reduce the probability of occurrence and to minimize the severity of harm when such events happen.

### Risk Causing Events in Compliance

All human activities and endeavors have risk associated with them. Drug product manufacturing has quite a bit of risk associated with them. There is always the risk that contamination of the drug during manufacturing will result in harm to the patient who would use the contaminated or adulterated drug. During drug manufacturing, the occurrence of certain events, if not detected and/or mitigated, is a guarantee that harm to the patient will occur. For example, microbial breakthrough in sterile filtration of an injectable could lead to the contamination of the drug. If this is not detected and mitigated prior to administering it to the patient, it would result in harm to the patients being treated with the drug.

The microbial breakthrough, discussed above, is referred to as a quality event in the context of Good Manufacturing Practice (GMP).



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Quality events vary depending on the expected conditions, the type of operation, and their closeness to the end product. There are two types of quality events associated with risk in GMP compliance, namely;

1. Negative quality events resulting in increased risk, including:
  - patient complaints or suffering during clinical trial
  - operating deviation or processing nonconformities in manufacturing
  - analytical results not meeting the expected outcome in the laboratory
  - excessive effort needed to meet regulatory requirements

Such quality events require immediate positive action on the part of the manufacturer.

2. Non-negative quality events potentially increasing risk, including:
  - patient complaints showing a negative trend in post approval use of the drug
  - operation drifting toward action limit
  - analytical data trending toward the unacceptable.
  - repeated need to make corrections
  - results suggesting a need for further investigation

Such quality events require increased scrutiny and the development of a response strategy.

In all cases, these events have to be reviewed to determine their risk implications and a study has to be performed to balance the risk-benefit factors prior to implementing the proper action.

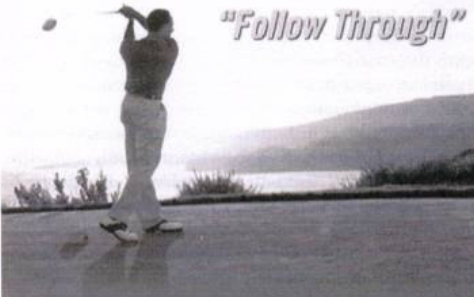
Risk in the manufacture of drug products ranges from a high or extreme risk level to a minimal or no risk level with the extreme having a "yes" and the minimal level having a "no" relationship to risk. In manufacturing, quality events are related to equipment and the operation of manufacturing systems. These go from the extreme of having direct impact on the product to the minimal of having no-impact on the product with several levels of having indirect impact on the product. The number of intermediate levels of risk varies from one organization or approach to another, and some organizations or risk assessment methodologies will identify three levels of risk, while others will identify as much as five.

Additional terminologies used to identify potential increased risk include critical system and non-critical systems, manufacturing equipment with product contact versus those without product contact. This is not to imply that non-product contact systems do not pose potential increased risk, but rather that issues associated with non-product contact equipment/systems are less severe and deserve less scrutiny than those associated with product contact equipment. Such terminology is important in defining compliance related activities.


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ties such as commissioning and/or validation, types of actions to be taken such as corrective or preventive actions, and levels of interference such as rework or recall.

The next question when looking at such events is to identify how the risk manifests itself.

### Risk Occurrence and its Manifestation

In the manufacture of drug products, some processes and/or operations are riskier than others. From a GMP point of view, the risk in these processes is dependent on the danger and its degree, which it poses to the public/patient when errors or defects occur and are not detected and addressed prior to distributing the product.

In the manufacture of drugs, the following processes/operations represent some of the riskiest in the business:

- sterile/aseptic processing
- potent compound processing
- labeling operations
- laboratory measurement errors
- operating errors in finishing operations
- automation systems, which rely on too many custom programs
- highly manual operations both in manufacturing and in record keeping

The risk associated with these operations manifests itself in many ways, including:

- contaminated drugs
- mislabeled drugs
- adulterated drugs
- drugs of the wrong potency (sub- or over potency)
- expired drugs
- nonconforming drugs
- non-performing drugs

Thus, it is incumbent on the GMP compliance practitioner to ensure that they are aware of all the risks associated with the operations they are responsible for. More importantly they should be aware of the way the risk manifests itself, ensuring a high level of detectability. Promptly addressing quality events as they occur and detecting the risk they pose are important components of any risk mitigating strategy.

Corrective actions as well as preventive actions are ways the drug industry uses to mitigate risk to the public. In order to develop the proper Corrective Action and Preventive Action (CAPA) quality system/strategy to mitigate risk, one needs to define and prioritize the risk levels in order to determine the proper action to be taken. Defining a Risk Probability Number (RPN) normally does this.

### Risk Levels and the Risk Probability Number (RPN)

In the manufacture of drug products, the level of risk for a quality event can be identified through combining the **Severity** of the harm to the patient, the **Frequency** by which the

event occurs, and the **Detectability** of the event. These three factors combined determine the level of risk either numerically or qualitatively as high, medium, or low. In order to reach a numerical value for the risk level, values to the three factors are assigned based on a company's experience with the product and the operation used to produce it. Multiplying the values for severity, frequency, and detectability results in a Risk Probability Number (RPN), which can be used to determine the appropriate Corrective and Preventive Action (CAPA) to be taken to address the quality event.

**Severity** of a given quality event is a measurement of the consequences of the event itself and its potential harm to the patient. The severity index ranges from events, which would result in a product causing death or serious injury to the patient (highest) to events causing no discomfort or delay of patient treatment (lowest).

**Frequency** of a given event defines the probability of its occurrence/reoccurrence. This is identified through reviewing the process history and acknowledging whether or not attempts were made in the past to reduce such frequency. The frequency index ranges from a certainty that the event will occur or has occurred frequently in the past (highest) to an event that is highly unlikely to occur or has been addressed in the past and preventive actions have been taken to prevent its reoccurrence (lowest).

**Detectability** is a measure of the probability that the quality event will be detected or its effect/result will be readily measured or seen. Here, events that are not detectable have the highest detectability index, while readily detectable events have the lowest detectability index.

Once the risk level for a quality event is determined, one needs to apply the principles of Q9, namely: "The degree of corrective and preventive action taken to eliminate or minimize actual or potential nonconformities must be appropriate to the magnitude of the problem and commensurate with the risks encountered." Thus, for low risk level events, normally no further investigation or corrective action is required. For medium risk level events, no further investigation (the cause is evident); however, corrective action is required. Finally, for high risk level events, further investigation (using Root Cause Analysis), corrective action, possibly immediate in the form of a recall, is required, and preventive action must be taken to ensure the event does not reoccur.

Based on this discussion, the risk level of a quality event occurring during sterile injectables manufacturing is very high, despite the fact that it does not occur frequently. This is due to the fact that it could lead to death (highest severity index) and is difficult to detect (highest detectability index). On the other hand, the risk level of an event occurring during the manufacture of an over the counter analgesic tablet is low even if it occurs frequently, because of the fact that its harm is low (low severity index) and its detectability is high (low detectability index).

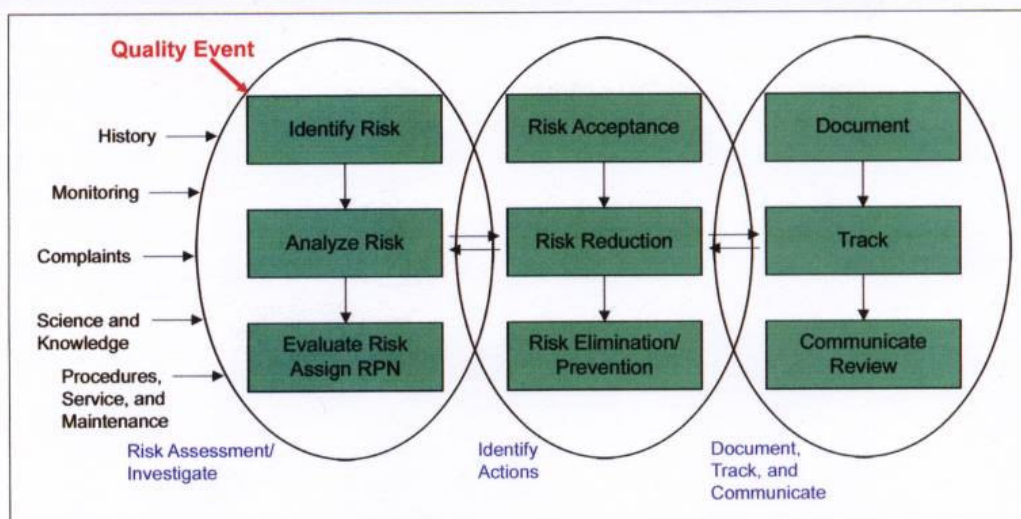


Figure 1. Overall approach for a robust CAPA Quality System.

### Corrective Action Preventive Action (CAPA) – Mitigating Risk in Compliance

Corrective Action Preventive Action (CAPA) is a quality system designed to mitigate risk in the manufacture of drugs and devices. ICH Q10<sup>3</sup> suggests that pharmaceutical companies “should have a system for implementing corrective actions and preventive actions... structured approach to the investigation process should be used with the objective of determining root cause.” As a risk mitigating quality system, CAPA addresses quality events, which occur during the manufacture of healthcare products. These could be a deviation, a failure to follow or implement an established requirement, a nonconformance failure to meet a specified requirement that occurs during the manufacture process. These quality events have the potential of posing a risk to the population and the need to mitigate their effect. In general terms, CAPA would define the risk resulting from such events and its level, identify an approach to mitigate such risk, implement the approach, and ensure its completion, while monitoring the implementation to ensure its success.

CAPA is a quality-based system, which uses deviations, nonconformances, and/or expectation of an event as the input to the system. It uses many of the quality procedures and systems already in existence within an organization to investigate and develop appropriate actions aimed at mitigating the risk. It also utilizes existing historical quality data, monitoring data, audit reports, service and maintenance records, product complaints, process knowledge, and operating procedures as a basis to identify risk and its level. Finally, once the actions identified are implemented, CAPA, by definition, has to track such implementation to ensure timeliness, correctness, and appropriateness.

In order to achieve its objectives, a CAPA program must

investigate the event, identify its consequences, and track the implementation of what specific action is implemented. So, CAPA investigates the cause and potential risk of a quality event as it relates to the product, process, and the quality system. Quality procedures used for such investigation include deviation reporting and investigation procedures and Out Of Specification (OOS) investigation procedures. CAPA also investigates the potential risk of an expected or contemplated event. It also uses tools such as HAZOP, HACCP, Failure Mode and Effect Analysis, Fault Tree Analysis, and “What If” scenarios to investigate level of risk of an event, its cause, and/or its “root cause.”

CAPA identifies the action needed to correct, reduce, or prevent recurrence of nonconformance of product and other quality problems. It also identifies the action needed to correct and prevent recurrence of the deviation in the operation as well as the action needed to prevent the potential occurrence of the anticipated quality event. These actions are generally referred to as corrective actions. Many of the corrective actions include one or several of the following:

- design changes
- manufacturing process changes
- removal of product from the market through recall
- operator training
- labeling changes
- patient education

It is of the utmost importance to recognize that whenever a change is contemplated, the change control procedure/system must be invoked. This will ensure that a record is maintained and that all quality, as well as GMP compliance implications, are reviewed and addressed.

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*“...CAPA is a quality assurance system, which addresses quality events, which may occur or could be anticipated to occur during healthcare products manufacturing.”*

Preventing the potential of deviations or nonconformances is also an objective of a robust CAPA program. Such measure is normally reserved for events, which have high Risk Probability Number (RPN).

Finally, CAPA tracks the implementation of the corrective/preventive action to ensure that the implementation of the action is completed on a timely basis and that introducing such changes do not introduce additional or new risk components. Tracking can be accomplished using appropriate procedures, while documenting everything associated with the event. Documentation of the event itself, the investigation and its findings, the action to be taken and timing for its implementation, closure of deviation or nonconformance are just some of the issues which must be tracked. Manual tracking represents challenges associated with generating too much paper, being cumbersome, time consuming, and providing limited access. Electronic tracking is becoming more and more common and eliminates many of the shortcomings of manual tracking. Today, there are several off-the-shelf products capable of providing such tracking functionality. However, these electronic tracking systems add the requirement of being 21 CFR part 11<sup>4</sup> compliant since they generate and maintain electronic records.

Figure 1 is a pictorial depiction of the general components of a CAPA System.

### CAPA: Example Implementation

One of the most important examples of applying a successful CAPA is associated with the Tylenol® scare of the 1980s. The quality event was the fact that capsules of an Over The Counter (OTC) analgesic formulation were laced with a poison and were eventually ingested by the public and resulted in the death of several persons. Upon recognizing the harm that occurred, the manufacture conducted investigation and recognized that the root cause was someone tampering with the capsules, while on the store shelves and laced them with poison in a random fashion. At that time, the manufacture used a nationwide recall of all encapsulated product as Corrective Action (CA). Based on further technical investigation, the manufacturer reached the conclusion that there is no way a capsule can be protected from future tampering by a determined person. Therefore, the Preventive Action (PA) taken by the manufacturer was to eliminate the use of capsules in Over The Counter (OTC) products and shifting to the use of caplets. Since that time, capsules were no longer used as a dosage form for OTC drugs.

Upon review of this incident, one would recognize that the severity of the quality event was at the highest possible level (results in death); thus, one could assign it the highest possible severity number. Although the quality event itself

would probably be infrequent with a finite probability that it will reoccur (it has occurred twice by that time giving it a frequency number that is relatively high), it would be very difficult to detect giving it the highest possible detectability number. The combination of highest severity, highest detectability, and high frequency number would result in a very high RPN suggesting the need for immediate corrective action (recall) and eventual preventive action (eliminating capsules as dosage form in OTC drugs).

This also suggests that although the term CAPA was not in wide use in the 1980s, many drug manufacturers had in house programs to address such eventualities. The example here shows that the manufacturer of the analgesic has implemented a quality approach that resulted in protecting the public and preventing further risk to its welfare. Articulating the program based on the ICH and FDA guidance helps formalize such an approach and ensures that all drug manufacturers implement it. This ensures a higher level of safety to the public and improves process and product quality for the entire industry.

### CAPA: System's Components and Specific Steps

Up to this point, the discussion has focused on risk in compliance and in a broad-brush fashion, the general approach of a CAPA program. The following discussion will review specific steps which must be taken when implementing a CAPA program.

As discussed above, CAPA is a quality assurance system, which addresses quality events, which may occur or could be anticipated to occur during healthcare products manufacturing. The system is based on reviewing the event and analyzing the risk associated with the event. It then assigns a Risk Probability Number (RPN) to the event upon which a decision is made to accept, reduce, or eliminate the risk all together. Once the decision is made, then appropriate action is taken. The event, the analysis, the decisions made, and action(s) taken are then documented, communicated, and tracked to ensure that they were correct, appropriate, and did not introduce different or additional variability/risk to the operation.

The quality event, either a deviation, a nonconformance, or an anticipated result is the input for a CAPA program. In order to perform the appropriate analysis of the event, one needs to review appropriate historic data, such as monitoring data, product complaint data, analytical data, scientific knowledge, previous process experience, etc. This review, combined with using the appropriate QA procedures existing within the organization (e.g., deviation reporting and investigation, OOS investigation, etc.) will define the risk and its implica-

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tion. Once a certain course of action to address the risk is identified, procedures such as maintenance, rework, and change control are utilized to implement the action.

Based on this discussion, the following represents proposed basic elements or steps for a CAPA program and how they would be implemented:

### 1. Label and Segregate Nonconforming Product

When a nonconformance occurs, the resulting product or material should be packaged, properly labeled (e.g. Hold, Reject, Quarantine), and stored separately in a segregated space with limited access.

### 2. Tag and Lock All Equipment Involved in the Event

Equipment which may have caused the problem or may have problems, also should be tagged indicating that they are suspect and locked to prevent further use until an investigation has taken place and a plan of action is established.

### 3. Document the Event or Issues

Record the nonconformance on the appropriate report forms (deviation, OOS, etc.). Ensure that all studies and decisions made are fully and properly documented.

### 4. Investigate and Evaluate

Review the event and the circumstances surrounding it. Document relevant details as part of the nonconformance or deviation report. Evaluate risk to quality and link it to protecting the patient. Use RPN to help determine need for in-depth investigation and Corrective/Preventive Action (i.e., the effort, formality, and documentation should be commensurate with the level of risk and be based on science).

### 5. Take Necessary Actions

Make necessary changes to reduce risk or eliminate it. Ensure that change control is invoked when needed. Track and evaluate the actions taken to ensure that no additional or different risk was introduced.

### 6. Record, Communicate, and Monitor

Record all actions taken and communicate the results throughout the organization. This ensures that other parts of the organization would not face the same problem by taking preventive action. Finally, carefully monitor the process to ensure that it has not been negatively affected by changes.

## Conclusion

In conclusion, quality events, which occur during the manufacture of health products, are always associated with a level of risk. A robust CAPA program is a regulatory requirement that defines the level of risk and how to mitigate it. However, one must note that implementing such a program is not limited to the regulatory imperative, but also makes good business and financial sense. A robust CAPA program would lead to better understanding of the process utilized and by identifying potential deleterious events that may occur and

addressing them a priori, thus optimizing its operation. Additionally, enhanced product and process understanding will result in improved product quality followed by improving its cost structure.

Moreover, implementing a CAPA program not only has such a potential positive economic impact on the manufacturing process, but also would lead to better customer satisfaction and reduces risk to the public, which is a major moral imperative. It also allows companies to better plan and use their resources through a structured QA system. CAPA systems facilitate a better and more informed decisions making process by manufacturers, and its existence improves a company's compliance quotient (i.e., makes a company look good to the regulators).

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## About the Author



**Gamal Amer, PhD** is Principal at Premier Compliance Services, Inc., management consultants for compliance and manufacturing operations performance in the life sciences industry. He holds a PhD in Chemical Engineering and has more than 25 years of experience in the pharmaceutical and related industries. He has held positions of increased responsibility with leading pharmaceutical, consumer product, and engineering consulting firms over the years. His experience includes comprehensive process design in bulk pharmaceutical manufacturing, biotechnology manufacturing, pharmaceutical solid dosage manufacturing, and containment of potent and radioactive therapeutics. He is also experienced with facility development for therapeutic products operations. Dr. Amer is a recognized expert in GMP compliance and validation. He has consulted for many of the leading pharmaceutical, biotechnology, and medical device manufacturers. He has lectured extensively in the US, Europe, Asia and the Middle East, taught many courses, and authored many papers which were published in peer reviewed publication. He is a member of ISPE, PDA, ACS, and AIChE. He can be reached by telephone: +1-610-584-9731 or by e-mail: [vpainc@aol.com](mailto:vpainc@aol.com).

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