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HOW TO IMPLEMENT AN EFFECTIVE NINE STEP PROGRAM

JACKELYN RODRIGUEZ

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CAPA in the Pharmaceutical and Biotech Industries

How to Implement an Effective Nine Step Program

Jackelyn Rodriguez

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Dedication

To
My Sons
Shaun, Berny, and Joseph.
This Book
Is
Affectionately and Lovingly Dedicated

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Contents

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Biography

Jackelyn Rodriguez is the President of Monarch Quality Systems Solutions, a consulting firm in New Jersey, and she is currently serving in a technical and regulatory compliance consultation capacity for several Medical Device, Pharmaceutical, Biologics, OTC Cosmetics and Compounding Pharmacy companies. Her consulting services place emphasis on all aspects of Quality Systems and Systems-based Implementation & Auditing, FDA Mock Inspections and Implementation of Risk Based programs. She has over 32 years of experience in all facets of Quality Assurance and Regulatory Compliance. She specializes in US Regulations and International Standards, which include FDA's QSR/GMPs 21 CFR Part 820, Parts 210 & 211, 503A 503B, 600 and Part 11 as well as ISO 9001/2000, 13485/2003, MDD/IMDD requirements, Canadian Regulation requirements, JPAL' MO no. 169 for Medical Device, Pharmaceutical and Biologics Industry. Her expertise encompasses Lean Manufacturing and Six-sigma Investigations and CAPA, Auditing, Process Validation, Document Control, Electronic Records/Electronic Signatures and Documentation Systems, Training and Learning Management Systems, Supplier Quality Assurance systems implementation, Quality Engineering, CE-Marking, Design Controls, Technical Files compilation, Risk Management/Hazard Analysis, Post-Market Surveillance and Vigilance as well as HIPAA requirements. Ms Rodriguez has been responsible for the creation and implementation of entire Quality Systems for numerous Device and Pharmaceutical companies. In addition to the above, Ms Rodriguez also possesses extensive knowledge of Compliance-Inspections and facilitating responses to address FDA-483s and Warning Letters.

Jackelyn has implemented numerous Audit Programs and has performed internal and external GMP/ISO and Clinical audits *of ongoing clinical trials in progress across organizations* (for both US and EU trials).

She has also completed several objective assessments of client documentation with respect to actual processes, systems and compliance to US FDA (medical device, Pharmaceutical, Biologics and Combination products), EU MDD/IMDD, and EMEA, ISO13485, ISO14971, JPAL, MDD/IMDD, ISO14155 (2011) requirements in order to address gaps and provide solutions for compliance. She has worked closely with CDRH's FDA HACCP team for both promotion of Risk Management and training of over 1000 individuals. Her wide-range of experience and recognized expertise have acquired her guest speaker positions worldwide, which include several FDA validation workshops. In addition to being and educational Instructor for several top institutions for almost 10 years, she provides training, consulting and advisory services to medical device, pharmaceutical, biologics, and biotechnology companies to ensure that the services are designed to leave systems and methodologies in place to establish a sustainable FDA and Compliance environment. Jackelyn holds a BS in Business Management and has served as a certified member of the Board of Examiners for the Malcolm Baldrige National Quality Award program. Ms Rodriguez has been ASQ Certified Quality Auditor and an RAB Lead Assessor. She has published numerous validation and compliance-related articles and has been a global industry speaker and presenter on several compliance topics.

Preface

This book is dedicated to all of the people who have taught me invaluable lessons throughout my career, which have shaped me into the person I am today. Mr Tony Bradley always believed in me and provided me with guidance. It is because of Tony's direction that I ended up in the right place at the right time. Since the day I met her, Ms Patrese Kirsch has always been there for me not matter what time of the day, and she can literally complete my sentences. To my spiritual teacher, Mr Mordechay Eldar, who has truly showed me that the way to becoming a better human being is by doing everything with higher consciousness. He has taught me that this is accomplished by treating others with respect and dignity and by always trusting that the light will guide me to provide the proper advice as a consultant, a parent, and now as an author. Last but certainly not least, this book is dedicated to my loving mother, who has taught me to be a strong dedicated and loving person.

This book describes "how" an effective and user friendly corrective actions and preventive actions (CAPA) program can be implemented and how the documentation needed to ensure that all CAPA requirements are fulfilled should be prepared. It also advises readers on how they can gain practical investigation experience to create successful root cause analysis. Not only does this book address how to understand the requirements for a closed loop CAPA system, but also covers topics such as organizational dynamics and culture and how to obtain CAPA system user buy-in, engage failure investigators interest, and practical tips for performing effective investigations.

Although many books and articles are there about CAPA programs and tips for performing root cause analysis, these books do not fully address how a company's current CAPA program can be enhanced, nor how the proper use of root cause analysis tools will ensure for a 100% complete and thorough investigation. This book will help to prepare the personnel involved in the CAPA and investigation process by teaching specific ways for all personnel to gain practical investigation experience. Thus, the book intends to help fill the gap with regard to continuous insufficiencies of investigational practices when it comes to CAPA. The examples included in this book are designed to have a practical and relatable appeal to all readers.

My hope is that this book will serve many purposes, but most importantly to promote an understanding of how to implement an effective and practical CAPA system and to conduct thorough investigations that will facilitate the creation of successful root cause analysis to prevent the occurrence of product and process failures. I hope this book can be used as a guide for creating and conducting ad-hoc instructional sessions on CAPA specific topics.

Jackelyn Rodriguez
Marlton, New Jersey, USA
November 2015

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Introduction

This book contains the most current information on how to implement, develop, and maintain an effective corrective action and preventive action (CAPA) and investigation program using a nine-step closed-loop process approach for medical device, pharmaceutical, and biologic manufacturers, as well as any company or institution that has to maintain a quality system.

Corrective and preventive action (CAPA)

> *According to the U.S. Food and Drug Administration (FDA), the purpose of a CAPA program is to collect information, analyze information, identify and investigate product and quality problems, and take appropriate and effective corrective and/or preventive action to prevent their recurrence*
>
> *(http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074883.htm).*

CAPA violations along with ineffective complaint investigations continue to be the main cited violation of device warning letters for the past 10 years, leading the FDA to remind firms to fully investigate complaints, find the root cause of nonconforming products, and document their CAPA activities.

A review of FDA warning letters issued to pharmaceutical companies reveals that most of these warning letters resulted from recurring failures, ineffective investigations found, and missing or inappropriate corrective and preventive actions. Companies often make the mistake of fixing problems in their processes by revising procedures or more commonly by "retraining" employees who may or may not have caused the problem. This is typically event-focused. Companies then will make the false assumption that the errors have been eradicated. In many cases they will also consider the steps taken as their preventive action. The reality is that the causes of the failure were never actually determined; therefore the same problem will recur over and over.

An effective CAPA program is a complete system that collects information regarding existing and potential quality problems. It analyzes and investigates the issues to identify the root cause of nonconformities. CAPA is not just a quick-fix, simple approach. It is a process and has to be understood throughout organizations.

Medical device, pharmaceutical, and biotechnology manufacturers continue to see recurring failures of product and process. These reoccurrence of these issues could be prevented, if only companies took the time. Issues are identified in many ways, including:

- Customer complaints
- Product defect

- Process failures
- Process deviations or exceptions
- Concessions
- Reworks
- Supplier quality issues
- Adverse event reporting
- Recalls

Inadequate investigations of these issues, in particular customer complaints, and the fact that in most cases companies do not perform a robust risk analysis against the type of failure, have resulted in a significant number of FDA 483 inspectional observations, warning letters and in some cases higher regulatory actions such as consent decrees, injunctions, prosecutions, and export bans. Most importantly, these regulatory actions continue to be escalated by the FDA because in most cases whenever a company submits a response to an FDA observation, typically the response does not include a true root cause analysis nor does it provide clear, objective evidence that the organization has handled and remediated corrections, implemented the appropriate corrective actions, and provided the plans for how the corrective actions will be verified to show effectiveness.

Although it is critical to have a central repository for the multiple sources of product, process, and quality issues, most companies segregate the issues by departments or areas of responsibility, and most often these departments or areas do not speak to each other and information is not shared; needless to say, this gets worse when it comes to multiple sites. Having a central location would allow all sources to have a single source of the issues, failures, and recurring problems. This allows you to manage the workflow around issue analysis, as well as tracking the active decision and rationale of whether or not to generate a CAPA.

Well-managed quality incidents do not always result in a CAPA, but if one is required, creation of the CAPA is the next step in the process flow management.

What is an appropriate CAPA program?

Since 2006, the FDA has reported that many companies do not employ effective CAPA systems. Typically, the FDA sees 30% to 50% nonconformance in any given warning letter. These are generally CAPA-related issues. In one of their meetings, the FDA noted that 76% of all warning letters for 2004 had CAPA-related issues. That is an overwhelming percentage, and it occurred because these companies did not do a good enough job not only of identifying corrective and preventive actions but of validating the effectiveness of their plans. They did not verify that the corrective actions they employed were actually effective.

A compliant CAPA system will include:

1. Tie-in risk analysis—failure mode, effects, and criticality analysis (FMECA), Fault Tree Analysis (FTA), etc.
2. Robust investigation, which includes getting to the root cause(s)
3. Effective corrective action verification
4. Preventive action program
5. Tie-in design control procedures
6. Tie-in process control procedures

Remember that CAPA procedures require analyzing processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product or other quality problems.

CAPA is a well-known current good manufacturing practice (CGMP) regulatory concept that focuses on investigating, understanding, and correcting the discrepancies while attempting to prevent their recurrence. Corrective action measures are taken to prevent the reoccurrence of the identified problem. Preventive action measures are taken to prevent the reoccurrence of a similar potential problem. Corrective action is a reactive tool for system improvement to ensure that significant problems do not recur.

It is essential to determine what actions will reduce the likelihood of a problem recurring. Examples of sources that can be used to gather such information include the following:

- Nonconformance reports and rejections
- Returns
- Complaints
- Internal and external audits
- Data and risk assessment related to operations and quality system processes
- Management review decisions

Regulated companies need to establish and maintain procedures for implementing corrective and preventive action. The procedures must include requirements for analyzing processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product or other quality problems. Appropriate statistical methodology should be employed where necessary to detect recurring quality problems.

- Investigating the cause of nonconformities relating to product, processes, and the quality system.
- Identifying the action(s) needed to correct and prevent recurrence of nonconforming product and other quality problems.
- Verifying or validating the corrective and preventive action 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.
- Ensuring that information related to quality problems or nonconforming product is disseminated to those directly responsible for assuring the quality of such product or the prevention of such problems.
- Submitting relevant information on identified quality problems, as well as corrective and preventive actions, for management review.

CAPA systems should be controlled by documented procedures and, at a minimum, should contain records for the following information: identification and description of each issue, when initiated, and where appropriate; the name of the individual or function initiating the need for CAPA; documentation of the analysis/investigations conducted for each issue; and identification of decision/rationale/approval for each issue or the decision not to pursue corrective action.

Closed-loop systems include the verification or validation of CAPA to ensure that the actions were conducted as documented, were effective, and did not have an adverse effect on products or systems. Communication of information related to corrective and preventive actions must be provided to those responsible for assuring the quality of affected product or the prevention of such issues. Communication should include a management review where appropriate.

Corrective and preventive actions should be initiated where appropriate, and followed through to completion. Such actions are commensurate with the urgency and magnitude of the risks involved. The CAPA system should ensure that data sources for product and process quality, or regulatory compliance, are identified and analyzed for negative trends or the existence of issues that require intervention. Typical data sources may include, but are not limited to:

- Complaints and/or complaint trend analysis
- FDA 483s, warning letters, or other regulatory actions
- Rejects and/or reject trend analysis
- Reworks
- Returned product processing and analysis
- Manufacturing process and/or work process monitoring data
- Training reports
- Document control records
- Customer feedback
- Lawsuits or other legal actions
- Quality audits (internal or external)
- Management review
- Suppliers
- Product recall
- Process control auditing
- Finished product auditing
- Adverse event investigation and reporting

Subprocesses to consider when gaining CAPA compliance should include:

- Documented preventive action.
- Link to management response.
- Appropriate statistical techniques (not just trend analysis). Do not forget part 11 and 21 CFR 820.70.i.
- Internal audits and regulatory inspections may lead to related CAPA actions.
- Risk management ISO 14,971 as occurrence of events increases.
- Design control and design changes triggered by CAPAs (especially device validation, complaints).
- FDA quality system regulation changes in regulatory requirements.

A CAPA system will include linkage to other quality systems programs such as:

- Preventive action program
- Tie-in design control procedures
- Tie-in process control procedures
- Tie-in risk analysis (FMECA, FTA, etc.)
- Risk analysis

Analyze data for trends

Quality systems call for continually monitoring trends and improving systems. This can be achieved by monitoring data and information, identifying and resolving problems, and anticipating and preventing problems.

Quality systems procedures involve collecting data from monitoring, measurement, complaint handling, or other activities, and tracking the data over time, as appropriate. *Analysis of data can provide indications that controls are losing effectiveness. The information generated will be essential to achieving problem resolution or problem prevention.*

Although a CGMP regulation (§ 211.180(e)) requires product review on at least an annual basis, a quality systems approach calls for trending on a more frequent basis as determined by risk. Trending enables the detection of potential problems as early as possible to plan corrective and preventive actions.

Another important concept of modern quality systems is the use of trending to examine processes as a whole; this is consistent with the annual review approach. Trending analyses can help focus internal audits.

Preventive actions

Being proactive is an essential tool in quality systems management. Succession planning, training, capturing institutional knowledge, and planning for personnel, policy, and process changes are preventive actions that will help ensure that potential problems and root causes are identified, possible consequences assessed, and appropriate actions considered. The selected preventive action should be evaluated and recorded, and the system should be monitored for the effectiveness of the action.

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Understanding the FDA's CAPA requirements and regulations

1

Part I. 21 CFR part 820.100 for medical devices

Exhibit 1.1 Overview of part 820.100 requirements

Subpart J. Corrective and preventive action
Section 820.100 Corrective and preventive action

1. Each manufacturer shall establish and maintain procedures for implementing corrective and preventive action. The procedures shall include requirements for:
   - **a.** Analyzing processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems. Appropriate statistical methodology shall be employed where necessary to detect recurring quality problems;
   - **b.** Investigating the cause of nonconformities relating to product, processes, and the quality system;
   - **c.** Identifying the action(s) needed to correct and prevent recurrence of nonconforming product and other quality problems;
   - **d.** Verifying or validating the corrective and preventive action to ensure that such action is effective and does not adversely affect the finished device;
   - **e.** Implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems;
   - **f.** Ensuring that information related to quality problems or nonconforming product is disseminated to those directly responsible for assuring the quality of such product or the prevention of such problems; and
   - **g.** Submitting relevant information on identified quality problems, as well as corrective and preventive actions, for management review.
2. All activities required under this section, and their results, shall be documented (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=820&showFR=1&subpartNode=21:8.0.1.1.12.10).

CAPA in the Pharmaceutical and Biotech Industries. http://dx.doi.org/10.1016/B978-1-907568-58-9.00001-1

Part II. 21 CFR Part 211: current good manufacturing practice for finished pharmaceuticals

Exhibit 1.2 Overview of part 211 requirements

Subchapter C. Drugs: general
Subpart B. Organization and personnel
Section 211.22 Responsibilities of quality control unit

1. There shall be a quality control unit that shall have the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated. The quality control unit shall be responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company.
2. Adequate laboratory facilities for the testing and approval (or rejection) of components, drug product containers, closures, packaging materials, in-process materials, and drug products shall be available to the quality control unit.
3. The quality control unit shall have the responsibility for approving or rejecting all procedures or specifications impacting on the identity, strength, quality, and purity of the drug product.
4. The responsibilities and procedures applicable to the quality control unit shall be in writing; such written procedures shall be followed (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=211.22).

Subpart J. Records and reports
Section 211.192 Production record review

All drug product production and control records, including those for packaging and labeling, shall be reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed. Any unexplained discrepancy (including a percentage of theoretical yield exceeding the maximum or minimum percentages established in master production and control records) or the failure of a batch or any of its components to meet any of its specifications shall be thoroughly investigated, whether or not the batch has already been distributed. The investigation shall extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy. A written record of the investigation shall be made and shall include the conclusions and follow-up (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=211.192).

Subpart J. Records and reports
Section 211.180 General requirements

5. Written records required by this part shall be maintained so that data therein can be used for evaluating, at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures. Written procedures shall be established and followed for such evaluations and shall include provisions for:
   a. A review of a representative number of batches, whether approved or rejected, and, where applicable, records associated with the batch.
   b. A review of complaints, recalls, returned or salvaged drug products, and investigations conducted under Section 211.192 for each drug product.

6. Procedures shall be established to assure that the responsible officials of the firm, if they are not personally involved in or immediately aware of such actions, are notified in writing of any investigations conducted under Sections 211.198, 211.204, or 211.208 of these regulations, any recalls, reports of inspectional observations issued by the Food and Drug Administration, or any regulatory actions relating to good manufacturing practices brought by the Food and Drug Administration (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=211.180).

Both quality systems and the CGMP regulations emphasize corrective actions. Quality systems approaches call for procedures to be developed and documented to ensure that the need for action is evaluated relevant to the possible consequences, the root cause of the problem is investigated, possible actions are determined, a selected action is taken within a defined timeframe, and the effectiveness of the action taken is evaluated. It is essential to document corrective actions taken (CGMP also requires this; see Section 211.192).

Part III. The FDA's current inspectional approaches

At one point or another, companies that manufacture products regulated by the U.S. Food and Drug Administration (FDA) will be inspected by the FDA, and it is very important for companies to understand the Code of Federal Regulations that may apply to the company, and also to understand the FDA's current inspectional approaches. The FDA's current inspectional approaches include the following:

- Quality systems inspectional technique (QSIT): medical devices
- Pharmaceutical Current Good Manufacturing Practices (CGMPs) for the Twenty-First Century Initiative quality systems approach to pharmaceutical current good manufacturing practice regulation: pharmaceuticals, biologics, compounding products, OTC (over-the-counter) products

Review of the quality system inspectional technique: medical devices

QSIT and CAPA

From the QSIT perspective, we know that when the FDA does a follow-up inspection, they have the mandate to establish a CAPA (Corrective and Preventive Actions) plus one for companies that are compliant, that is, if the company has no Warning Letters or regulatory issues with the FDA. That is the standard system of doing an inspection. They perform an inspection using the QSIT approach and always start with CAPA when it is a surveillance inspection. The FDA will always look at those elements of a CAPA program. For this reason, it is very important to become familiar with the QSIT approach and to read the QSIT Handbook.

Elements of the handbook are too lengthy to review here. However, the author/presenter strongly suggests that the reader download the handbook to understand the elements and objectives that the FDA looks at during a QSIT inspection. Pay particular attention to the FDA objectives on inspection items used for facility inspection to understand whether your company is collecting the right information, analyzing the right information, identifying the quality indicators that the FDA uses, and taking the appropriate corrective and preventive actions.

You will also read there how the FDA follows up and verifies effectiveness. Within the purpose of the QSIT Handbook approach from a CAPA perspective, there are several inspectional elements that the FDA considers when they are looking at the CAPA subsystems, and it would be well worth your time to review the handbook for these particulars to understand the FDA's thought processes. The review of QSIT will give the reader some insight into the requirements from the QSIT inspection prospective, which can be very helpful.

QSIT is based on the theory that there are seven subsystems in the quality system:

- Corrective and preventive actions
- Design controls
- Production and process controls
- Management controls
- Records/document/change controls
- Materials controls
- Facility and equipment controls

What is QSIT?

QSIT moves the FDA closer to the Global Harmonization guideline for regulatory auditing of quality systems of medical device manufacturers, and it incorporates the seven subsystems concept, which provides specific guidance on auditing each subsystem.

QSIT is an inspection process based on the subsystems of the quality system. It has been suggested that a quality system can be broken down into seven subsystems, in the following order:

- Management responsibility
- Design controls
- Production and process controls
- Corrective and preventive actions
- Records, documents, and change controls
- Materials controls
- Facilities and equipment
- *Cite detailed evidence where systems or processes are not working*

To improve the efficiency of the inspection process, the QSIT approach focuses on the four primary subsystems: management controls, design controls, corrective and preventive actions, and production and process controls.

The other three subsystems—such as material controls; records, documents, and change controls; and equipment and facilities controls—are addressed by QSIT through linkages rather than through specific coverage.

As indicated in the guide, linkages allow the investigator to leave a subsystem in order to cover another aspect of the quality system. They are used because subsystem probes cannot be performed exclusive of other aspects of the system.

The question that most companies often have is how will management be inspected? Well, that all depends on the type of inspection. Exhibit 1.3 shows the types of inspections that the FDA could perform based on the FDA's Compliance Program 7382.845 t.

As you can see, even if it is an abbreviated inspection, there is always a requirement to review the CAPA subsystem plus another subsystem. Which second subsystem? The answer will be based on what the investigator discovers in CAPA.

Exhibit 1.3 Compliance program 7382.845 t

Inspection level	Type of inspection	Guide to inspections
1	Abbreviated	QSIT—Two subsystems: Corrective and preventive actions (CAPA) plus production and process controls (P&PC) or design controls (PAC 82845A)
2	Comprehensive	QSIT—the four major subsystems: management controls, design controls, CAPA, and P&PC (PAC 82845B or 82845P or 82A800)
3	Compliance follow-up	As directed by inspectional guidance and elements of QSIT (PAC 82845C)
Special	For cause	As directed by inspectional guidance and elements of QSIT (PAC 82845G)
Special	Risk-based work plan	As directed by CDRH inspectional assignment and elements of QSIT (PAC 82845H)

Fact: The only subsystem of a facility quality system that the FDA "always" examines at inspections is the corrective and preventive action program. The FDA's inspection approach could include:

- A combination of the traditional approach and QSIT.
- A combination of "bottom-up" and "top-down" approaches.
- Start with complaints, CAPA, nonconformances.
- Look back two years.
- What really happens? Follow the threads!
- Complaints review: MDRs submitted? Timely?
  - What are the trends? Does the company trend data? How are the data used?
  - Electronic record request?
- Nonconformance system: what are the trends? How are these related to complaints, product, and design?
- CAPA: how many open? Closed? Timely? Root cause investigations? Adequate? Effective? Verification/validation?
- Does the company have a system outside of CAPA? Quality goals, "projects," internal audits?
  - Do complaints, Non Conforming Reports (NCRs) escalate to CAPAs?
  - Trending quality data.
- Supplier quality: Process, qualified, scars? Information from other subsystems?

Part IV. QSIT and CAPA: inspectional objectives

Purpose/importance

The purpose of the corrective and preventive action subsystem is to collect information, analyze information, identify and investigate product and quality problems, and take appropriate and effective corrective and/or preventive action to prevent their recurrence. Verifying or validating corrective and preventive actions, communicating corrective and preventive action activities to responsible people, providing relevant information for management review, and documenting these activities are essential in dealing effectively with product and quality problems, preventing their recurrence, and preventing or minimizing device failures. One of the most important quality system elements is the corrective and preventive action subsystem (http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074883.htm).

The following is a list of inspectional objectives that an FDA investigator will follow whenever QSIT is used to inspect a medical device facility. Although the QSIT inspectional handbook was written for medical devices, the same inspectional objectives are used for other areas such as Pharma, biologics, OTC cosmetics, and so forth.

The first thing that the investigator will do is to verify that CAPA system procedure(s) that address the requirements of the quality system regulation have been defined and documented.

Review the firm's corrective and preventive action procedure. If necessary, have management provide definitions and interpretation of words or terms such as "nonconforming product," "quality audit," "correction," "prevention," "timely," and others. It is important to gain a working knowledge of the firm's corrective and preventive action procedure before beginning the evaluation of this subsystem.

Corrective actions taken to address an existing product or quality problem should include actions to correct the existing product nonconformity or quality problems and prevent the recurrence of the problem.

An effective CAPA procedure should include procedures for how the manufacturer will meet the requirements for all elements of the CAPA subsystem. All procedures should have been implemented.

Once the investigator has gained knowledge of the manufacturer's corrective and preventive action procedure, he or she will begin with determining if the manufacturer has a system for the identification and input of quality data into the CAPA subsystem. Such data include information regarding product and quality problems (and potential problems) that may require corrective and/or preventive action.

The investigator will try to determine if appropriate sources of product and quality problems have been identified, and confirm that data from these sources are analyzed to identify existing product and quality problems that may require corrective action.

Companies should have methods and procedures to input product or quality problems into the CAPA subsystem. Product and quality problems should be analyzed to identify product and quality problems that may require corrective action. This should also be part of the company's CAPA procedures, and the company should routinely analyze quality data regarding product and quality problems. This analysis should include data and information from all acceptance activities, complaints, service, and returned product records.

The investigator will try to determine if the manufacturer is capturing and analyzing data from acceptance activities relating to component, in-process, and finished device testing. Information obtained subsequent to distribution, which includes complaints, service activities, and returned products, as well as information relating to concessions (quality and nonconforming products), quality records, and other sources of quality data, should also be captured and analyzed. Examples of other sources of quality data include quality audits, installation reports, and lawsuits.

The investigator will try to determine if sources of product and quality information that may show unfavorable trends have been identified. Confirm that data from these sources are analyzed to identify potential product and quality problems that may require preventive action.

The investigator will try to determine if the manufacturer is identifying product and quality problems that may require a preventive action. This can be accomplished by reviewing historical records such as trending data, corrective actions, acceptance activities (component history records, process control records, finished device testing, etc.) and other quality system records for unfavorable trends.

The investigator will review whether or not preventive actions have been taken regarding unfavorable trends recognized from the analysis of product and quality information. Product and quality improvements and use of appropriate statistical process control techniques are evidence of compliance with the preventive action requirement.

The investigator will try to determine if the manufacturer is capturing and analyzing data regarding in-conformance product. Examples include capturing and analyzing component test results to detect shifts in test results that may indicate changes in vendor processes, component design, or acceptance procedures. Monitoring in-process and finished device test results may reveal additional indicators of potential quality problems.

The investigator will try to determine if the manufacturer is using statistical control techniques for process controls where statistical techniques are applicable. An example would be Statistical Process Control (SPC). SPC is utilized to monitor a process and initiate process correction when a process is drifting toward a specification limit. At one point the investigator will try to challenge the quality data information system. And the inspector will try to verify that the data received by the CAPA system are complete, accurate, and timely.

The investigator will try to verify that appropriate statistical methods are employed (where necessary) to detect recurring quality problems. The investigator will determine if results of analyses are compared across different data sources to identify and develop the extent of product and quality problems. The analysis of product and quality problems should include appropriate statistical and nonstatistical techniques. Statistical techniques include Pareto analysis, spreadsheets, and pie charts. Nonstatistical techniques include quality review boards, quality review committees, and other methods. The analysis of product and quality problems should also include the comparison of problems and trends across different data sources to establish a global, and not an isolated, view of a problem. For example, problems noted in service records should be compared with similar problem trends noted in complaints and acceptance activity information.

Note: It is critical to emphasize that the FDA will always look at the full extent of a problem to be captured before the probability of occurrence, risk analysis, and the proper course of corrective or preventive action can be determined, and the investigator will try to determine if failure investigation procedures are followed. Determining the degree to which a quality problem or nonconforming product is investigated is commensurate with the significance and risk of the nonconformity. Most importantly, the investigator will try to confirm if failure investigations are conducted to determine the root cause (where possible).

The investigator will review the manufacturer's CAPA procedures for conducting failure investigations. The investigator will determine whether the procedures include provisions for identifying the failure modes, the significance of the failure modes (using tools such as risk analysis), the rationale for determining if a failure analysis should be conducted as part of the investigation, and the depth of the failure analysis.

The investigator will try to determine whether the depth of the investigation (where possible) is sufficient (root cause) to determine the corrective action necessary to correct the problem, and the investigator will select one significant failure investigation that resulted in a corrective action and determined if the root cause had been identified so that verification or validation of the corrective action could be accomplished.

The investigator will review controls for preventing distribution of nonconforming products. Product and quality concessions should be reviewed to verify that the concessions have been made appropriate to product risk, within the requirements of the quality system and not solely to fulfill marketing needs.

The investigator will try to determine if corrective and preventive actions were effective and verified or validated prior to implementation. The investigator will also confirm that corrective and preventive actions do not adversely affect the finished device.

The investigator will select a sample of significant corrective and preventive actions, determine the effectiveness of these corrective or preventive actions, and try to determine if there are any similar product or quality problems after the implementation of the corrective or preventive actions. And the investigator will determine if the manufacturer verified or validated the corrective or preventive actions to ensure that such actions are effective and do not adversely affect the finished device.

The investigator will verify that corrective and preventive actions for product and quality problems were implemented and documented, and if information regarding nonconforming product and quality problems and corrective and preventive actions has been properly disseminated, including dissemination for management review.

Part V. Quality systems approach to pharmaceutical current good manufacturing practice regulation, September 2006

Background

In August 2002, the FDA announced the Pharmaceutical CGMPs for the Twenty-First Century Initiative

The agency's intent is to integrate quality systems and risk management into existing programs.

The goal is to encourage the adoption of modern and innovative manufacturing technologies. The agency also saw a need to address the harmonization of CGMPs and other non-U.S. pharmaceutical regulatory systems as well as the FDA's own medical device quality systems regulations with the new Six System Inspection Model. The key concepts of the model are:

- Quality
- Quality by design and product development
- Risk management and risk assessment
- *CAPA (corrective and preventive action)*
- *Change control*
- The quality unit

CGMPs and the concepts of modern quality systems

Several key concepts are critical for any discussion of modern quality systems. The following concepts are used throughout this guidance as they relate to the manufacture of pharmaceutical products.

1. Quality.
2. Quality by design and product development and quality by design.
3. Quality risk management.
4. CAPA.
    a. CAPA is a well-known CGMP regulatory concept that focuses on investigating, understanding, and correcting discrepancies while attempting to prevent their recurrence. Quality system models discuss CAPA as three separate concepts, all of which are used in the guidance.
    b. Remedial corrections of an identified problem.
    c. Root cause analysis with corrective action to help understand the cause of the deviation and potentially prevent recurrence of a similar problem.
    d. Preventive action to avert recurrence of a similar potential problem.
5. Change control.
6. The quality unit.

Review of the concept of corrective action

Corrective action is a reactive tool for system improvement to ensure that significant problems do not recur. Both quality systems and the CGMP regulations emphasize corrective actions. Quality systems approaches call for procedures to be developed and documented to ensure that the need for action is evaluated relevant to the possible consequences, the root cause of the problem is investigated, possible actions are determined, a selected action is taken within a defined timeframe, and the effectiveness of the action taken is evaluated. It is essential to document corrective actions taken (CGMP also requires this; see Section 211.192). It is essential to determine what actions will reduce the likelihood of a problem recurring. Examples of sources that can be used to gather such information include the following:

- Nonconformance reports and rejections
- Returns complaints
- Internal and external audits
- Data and risk assessment related to operations and quality system processes
- Management review decisions

Preventive actions

Being proactive is an essential tool in quality systems management. Succession planning, training, capturing institutional knowledge, and planning for personnel, policy, and process changes are preventive actions that will help ensure that potential problems and root causes are identified, possible consequences assessed, and appropriate actions considered.

The selected preventive action should be evaluated and recorded, and the system should be monitored for the effectiveness of the action. Problems can be anticipated and their occurrence prevented by reviewing data and analyzing risks associated with operational and quality system processes, and by keeping abreast of changes in scientific developments and regulatory requirements.

Promote improvement

The effectiveness and efficiency of a quality system can be improved through the quality activities described in this guidance. Management may choose to use other improvement activities as appropriate. It is critical that senior management be involved in the evaluation of this improvement process. The following table shows how the CGMP regulations correlate to specific elements in the quality systems model for this section. Manufacturers should always refer to the specific regulations to make sure they are complying with all regulations http://www.fda.gov/downloads/Drugs/.../Guidances/UCM070337.pdf.

Part VI. ISO 13485 and CAPA: inspectional objectives

Most countries in the world, including the European Union, for the conformity assessment of medical devices to be used by the company's management team, assess whether a quality system that can continuously manufacture and supply safe products is established and maintained. In addition, after the product is approved through the conformity assessment process, in order to evaluate the effectiveness of the conformity, the quality system of the manufacturer is regularly audited. The standard that is applied during the audit is ISO 13485. The FDA, like regulatory agencies in other countries, requires a quality system for medical devices administered by the FDA, and that quality system is called current good manufacturing practice (CGMP). The requirements of CGMP are defined in Part 820 of the Code of Federal Regulations Title 21, and these are the quality system regulations (QSR) of the FDA. When it amended the CGMP in 1990, the FDA made certain that it harmonized with international standards as much as possible. The following is a list of requirements for CAPA under the ISO 13485.

Measurement, analysis, and improvement

General

1. The organization shall plan and implement the monitoring, measurement, analysis, and improvement processes needed:
   a. To demonstrate conformity of the product.
   b. To ensure conformity of the quality management system.
   c. To (continually improve) maintain the effectiveness of the quality management system.
2. This shall include determination of applicable methods, including statistical techniques, and the extent of their use.

Monitoring and measurement

(Customer satisfaction) feedback

The organization shall establish a documented procedure for a feedback system to provide early warning of quality problems and for input into the corrective and preventive action processes (see Sections Corrective action and Preventive action).

Monitoring and measurement of processes

1. The organization shall apply suitable methods for monitoring and, where applicable, measurement of the quality management system processes.
2. These methods shall demonstrate the ability of the processes to achieve planned results.
3. When planned results are not achieved, correction and corrective action shall be taken, as appropriate, to ensure conformity of the product.

Control of nonconforming product

1. The organization shall ensure that product that does not conform to product requirements is identified and controlled to prevent its unintended use or delivery.
2. The controls and related responsibilities and authorities for dealing with nonconforming product shall be defined in a documented procedure.
3. The organization shall deal with nonconforming product by one or more of the following ways:
   a. By taking action to eliminate the detected nonconformity.

   b. By authorizing its use, release, or acceptance under concession (by a relevant authority and, where applicable, by the customer).
   c. By taking action to preclude its original intended use or application.

Analysis of data

1. The organization shall establish documented procedures to determine, collect, and analyze appropriate data to demonstrate the suitability and effectiveness of the quality management system and to evaluate where continual improvement of the effectiveness of the quality management system can be made. This shall include data generated as a result of monitoring and measurement and from other relevant sources.
2. The analysis of data shall provide information relating to:
   a. (Customer satisfaction) feedback (see 8.2.1).
   b. Conformity to product requirements (see 7.2.1).
   c. Characteristics and trends of processes and products including opportunities for preventive action.
   d. Suppliers.

Improvement

Continual improvement: general

1. The organization shall continually improve, or identify and implement, any changes necessary to ensure and maintain the continued suitability and effectiveness of the quality management system through the use of the quality policy, quality objectives, audit results, analysis of data, corrective and preventive actions, and management review.

Corrective action

1. The organization shall take action to eliminate the cause of nonconformities in order to prevent recurrence.
2. Corrective actions shall be appropriate to the effects of the nonconformities encountered.
3. A documented procedure shall be established to define requirements for:
   a. Reviewing nonconformities (including customer complaints).
   b. Determining the causes of nonconformities.
   c. Evaluating the need for action to ensure that nonconformities do not recur.
   d. Determining and implementing action needed, including, if appropriate, updating documentation (see 4.2).
   e. (Records) recording of the results of any investigation and of action taken (see 4.2.4).
   f. Reviewing the corrective action taken and its effectiveness.

Preventive action

1. The organization shall determine action to eliminate the causes of potential nonconformities in order to prevent their occurrence.
2. Preventive actions shall be appropriate to the effects of the potential problems.
3. A documented procedure shall be established to define requirements for:
   a. Determining potential nonconformities and their causes.
   b. Evaluating the need for action to prevent occurrence of nonconformities.
   c. Determining and implementing action needed.
   d. Reviewing preventive action taken and its effectiveness.

Summary to part VI

Although the ISO standard calls out for "measurement, analysis, and improvement," at the end of the day, the requirements are almost identical to the FDA's CAPA requirements. If a company complies with one or the other, the company could easily comply with U.S. and European Union CAPA requirements.

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Implementing a CAPA program: going back to basics

2

Corrective and preventive actions

This chapter will describe the basic principles and requirements of the Corrective and Preventive Actions (CAPA) process within a company. In addition, the chapter covers the process for the correction, prevention, review, and management of events and trends identified with products, processes, and/or quality systems. In addition, it will provide some insight into the differences between the definitions for correction corrective and preventive actions.

General requirements

A company must establish requirements for the following general matters:

- Quality data sources, their ownership, method of evaluation, and reporting, as per the CAPA and a Data and Analysis Procedure.
- Correction/remedial action and impact/risk-evaluation techniques to ensure that investigations and corrective/preventive actions are performed at a level commensurate to the risk, as per the Nonconformance Risk-Evaluation Process. As well as, the impact to the user (patients, users, product, etc.), which could result in a correction and removal.
- Investigation conducted to a degree sufficient to determine appropriate corrective actions or preventive actions, as per a company's Investigation Procedure.
- Frequency of CAPA review meetings. The frequency of the review must be established, and in most cases these meetings should be held monthly. In addition to the standard frequency, ad hoc reviews may also be planned as needed based on the following criteria:
  - Urgency (the issue cannot wait until the next standard meeting)
  - Requests from management

Ad hoc reviews should have an agenda limited to the issues that need urgent attention and for which the review is planned. The exact dates, time and duration, location, and agenda need to be established in advance and communicated to all participants.

CAPA process

The CAPA process needs to be established by applying the following steps:

1. Data collection
2. Identification (of quality events) for both Corrective and Preventive programs
3. Remedial action
4. Evaluation (including risk evaluation for product quality events)

CAPA in the Pharmaceutical and Biotech Industries. http://dx.doi.org/10.1016/B978-1-907568-58-9.00002-3

5. Investigation (to identify the need for root cause analysis and problem causes)
6. Management of (individual) CAPA (including action items as a result of the investigation)
7. CAPA data analysis
8. CAPA system review
9. Effectiveness checks

Quality data sources

The CAPA system is designed to achieve consistency in the approach, evaluation, analysis, and reporting of quality metrics from quality data sources/systems. The CAPA and Data and Analysis Procedures must specify the requirements for collecting and analyzing data from the CAPA system. The following list gives examples of quality data sources:

- Complaints, MDR, MDV, and other vigilance reports
- Service reports
- Quality Control (QC) Hold
- Corrections/removals
- Nonconformance control
- Audits (internal/external)
- Supplier audits
- Deviations and/or concessions
- Investigations
- Training
- Incoming inspection
- In-process inspection
- Final product inspection
- Process control and monitoring
- Environmental control
- Maintenance
- Calibration
- Validation
- Change control
- Product design (design transfer)
- Productions trends/data (e.g., process scrap, reworking)
- Management review meetings
- Out of Specification (OOS)
- Deviations
- Reworks
- Adverse drug events
- Medical device reports
- Recalls/corrections and removals

Correction/remedial action

A correction/remedial action has to be taken to alleviate the symptoms of an existing nonconformance or any other undesirable situation. Correction/remedial actions could include items such as reworking, scrap, products put on hold, separated or recalled, production or machine stoppages, retraining of an individual, or performing corrective maintenance.

Note: Depending on the risk associated with an event, not all issues require corrective action beyond immediate action. The investigation level should be based on a risk evaluation procedure.

Evaluation of risk

The evaluation of risk for product-related quality events facilitates decision-making and justification for the depth and extent of investigation and corrective/preventive action necessary in response to the event. It also helps management to properly prioritize investigative actions and corrective/preventive actions.

Note: Risk evaluation should be performed on quality events that have a direct impact on the distributed products.

The detailed steps for determining risk evaluations for quality events should be outlined in either a Nonconformance or Risk-Evaluation Process Procedure. That procedure should specify the requirements to designate qualified individuals to perform risk evaluations.

Quality event risk-evaluation process

- The identified quality event should be evaluated to determine the related risk to the patient, user, and third party:
  - This is typically determined by establishing the severity, frequency of occurrence, and detectability of a quality event. This activity results in a risk priority level.
- Determine action required as indicated by the risk priority level:
  - "Unacceptable" requires mandatory mitigation.
  - "Marginally acceptable" requires some level of activity, such as conducting reasonable, practical remedial action or mitigation, or justification for not taking any action.
  - "Acceptable" requires no further justification or mitigation.
- Determine the need for investigation:
  - "Unacceptable" requires mandatory root cause investigation.
  - "Marginally acceptable" requires some level of investigation.
  - "Acceptable" requires no investigation.

Investigation to identify problem cause(s)

If, based on the nonconformance risk-evaluation results, an investigation is required, then responsibilities are assigned to an "investigation owner" by a designated individual, and a plan for the investigation is established by this assigned individual. The planned investigation must be appropriate to identify the need and nature of CAPA as per the investigation (please refer to Chapter 8 for additional guidelines on the investigation process).

Management of CAPA

When the result of the investigation requires initiation of CAPA, the CAPA activities should be managed appropriately as follows.

Initiation of CAPA

The following CAPA information should be documented in the CAPA form (see Exhibit 2.1).

- Unique identifying number for the CAPA
- Revision level of the CAPA
- Date of initiation
- Initiator
- Product or process involved (part number/catalog number/other identification of item)
- Description of the quality event associated with the CAPA (details of reason for CAPA)
- CAPA source category (e.g., complaints, management review meeting, Non Conforming Reports (NCR))
- Reference to the investigation report
- Risk-evaluation number

This information should be inserted also in the companies CAPA database. The CAPA database should contain the basic information in order to trace the development of the activities. Each CAPA should be identified with a unique number.

The database could consist (at least) of the following fields:

- Unique identifying number for the CAPA
- Revision level of the CAPA
- Date of initiation
- Initiator
- Product or process involved (part number/catalog number/other identification of item)
- Description of the quality event associated with the CAPA (details of reason for CAPA)
- CAPA source category (e.g., complaints, management review meeting, NCR)
- Reference to the investigation report
- Risk-evaluation number
- CAPA owner
- CAPA plan (CAPA)
- Expected closure date of the activities described in the CAPA plan
- Expected closure date of the effectiveness verification
- Effective closure date of the activities described in the CAPA plan
- Effective closure date of the effectiveness verification
- Risk-evaluation number after the completion of the CAPA plan
- Notes and updating by the CAPA coordinator

The CAPA database is typically controlled and managed by a CAPA coordinator or a CAPA manager. The CAPA database should be in an electronic file so that the company can easily access and use the database to extract trend data.

Cross-reference to other CAPAs

The CAPA initiator should determine if a corrective/preventive action has been previously assigned that also applies to the current event. If so, then the CAPA initiator should cross-reference the previously assigned CAPA number on the new CAPA and could close it out. Previously assigned CAPAs should only be referenced if the CAPA coordinator, or designate, agrees that the assignment and the investigation are appropriate and if this is documented on the CAPA form.

CAPA plan

The CAPA coordinator (or designee) should enter the CAPA information into the CAPA database.

The CAPA coordinator or the CAPA review board typically will assign a CAPA owner to develop a CAPA plan, including the identification of resources required. This plan should be submitted to the CAPA review board for approval.

The CAPA owner develops the CAPA plan based on the event, the results in the investigation and root cause analysis report, and the related risk analysis. The identified risk levels should be used as drivers to identify priorities and time needed for the CAPA implementation.

The CAPA owner should document the CAPA plan with any needed attachments. The documentation should include the following:

- Description of the quality event
- Results of risk analysis
- Investigation results
- Explanation of why the C/CA/PA will address the identified events
- Description of activities required to implement the CAPA with due dates and responsibilities.
- Effectiveness check criteria and due date (methods and acceptance/verification criteria to determine effectiveness of corrective action and identification of the period for effectiveness verification)
- CAPA implementation team members

The CAPA plan

Each plan should be identified by the file name and a revision number. Any updating of an existing CAPA plan is identified via the updating of the date, and of the filename. Any change in the CAPA plan or any CAPA plan extension should be documented via a change in the revision number.

CAPA review board approval

The CAPA owner should submit the CAPA plan to the CAPA review board for approval, and the review board considers the following when approving the CAPA plan:

- The CAPA plan was developed to the level and extent required by the risk evaluation.
- The timing for completion of the CAPA is consistent with the risk analysis.

The review board should approve any CAPA plan extensions. The approvals for CAPA plan date extensions should be made prior to the expiration of existing plan dates. The CAPA review board approval must be documented in the CAPA plan form.

If the review board rejects the CAPA plan, then the CAPA owner should resubmit a revised CAPA plan by amending the original CAPA. This decision needs to be documented in the CAPA form and the revision level of the CAPA should be updated.

Implementation/execution

In most cases, the CAPA owner is responsible for ensuring the execution of the CAPA plan. Data generated during the execution of the plan should be verified by the CAPA owner or designee for the accuracy and correctness of the data and should attach a summary of the data or, can reference the place where the data resides (data summary or reports can be referenced if data files are too extensive to attach). The date that the CAPA has been implemented should be reflected in the CAPA database by the CAPA coordinator.

Effectiveness check

- The CAPA owner demonstrates effectiveness of the CAPA by verifying that the acceptance criteria are met. The acceptance criteria need to be established up front and should include valid statistical rational, such as the number of lots, time frame, who will be performing the verification, when, and where, as well as verification effectiveness records.

The CAPA owner or designee should provide objective evidence of completion in a completion report. The CAPA coordinator or designee must review the completion report and approves the report, if accepted. This approval needs to be documented.

Updating the risk evaluation

An update to the risk evaluation is required to demonstrate that the corrective action has had a positive result and did not have any adverse effects. The updated risk-evaluation number is to be inserted in the database by the CAPA coordinator.

CAPA closure

The CAPA coordinator should close the CAPA report after verifying that:

- The report is complete and contains all required information.
- The effectiveness check is done.
- The risk evaluation is updated.

Final closure should be obtained from an authorized individual assigned by the CAPA review board.

This approval is documented in the CAPA form. The CAPA coordinator closes the CAPA and updates the CAPA database and the original, completed CAPA reports could be filed in the archives of the CAPA coordinator.

If the CAPA is rejected, an updated CAPA plan should be defined and approved. This decision is documented in the CAPA form and the revision level of the CAPA should be updated.

Documentation

In order to manage all relevant CAPA activities, the following lists must be established:

- List of data sources
- Log file (list) of investigation with reference to the CAPA list as per investigation procedure
- Log file (list) of CAPA as per the CAPA form and the CAPA database or logs
- Link to any remedial actions including: corrections and removals

CAPA data analysis

A company must develop the specific procedure for CAPA data and analysis that identifies the following elements:

- Metric/owner
- Purpose of metric
- Frequency of reporting
- Method of presentation
- CAPA triggers and the elevation to CAPA

Typically the data owners should review the sources of conforming and nonconforming quality data, identify quality events, perform trends analysis, and report the results of that analysis to the CAPA review board. The analysis should contain sufficient information about the data to allow the CAPA review board to make informed decisions.

CAPA data should be analyzed and forwarded to the CAPA system review meetings. The results of the analysis and any further decision to take action should be recorded in the meeting minutes from the CAPA system review meeting. Items requiring further action must be elevated to the management review.

CAPA process metrics

- Metrics collected from the CAPA process must be identified in the corrective and preventive action or a data and analysis procedure.
- The CAPA coordinator (or designee) is typically responsible to produce reports that contain metrics and analysis in order to determine if further action is required as defined in a corrective and preventive action or data and analysis procedure.
- Reports should be reviewed at CAPA system review meetings.

Closed-loop corrective action

- The CAPA process data should be analyzed and forwarded to the CAPA system review meetings. The results of this analysis, and any further decision to take action, should be recorded in the meeting minutes from the CAPA system review meetings.
- Items requiring further action should be elevated to the management review.

CAPA review board actions

The CAPA review board should:

- Conduct periodic review of product and process data and information.
- Ensure resources are assigned as required to complete corrections, investigations, corrective actions, preventive actions, and the verification of effectiveness.
- Assign priorities for investigations and other special studies and CAPAs.
- Recommend product and process improvements.
- Follow up to assure that the corrective actions were implemented and are effective, that is, closed loop. The company's quality or regulatory management should be notified of potential

health or safety issues associated with distributed products, and should require immediate investigation and handling in accordance with the company's correction and removal procedure(s).

Interface with management review

As an essential requirement, executive management conducts management review meetings to a depth sufficient to determine if the quality system, organization structure, and resources are adequate.

All essential information derived from the CAPA system should be reported to the company's executive management on an ongoing basis so that appropriate resources can be allocated in order to prevent nonconforming events.

The following exhibit shows recommended fields for a CAPA form.

Exhibit 2.1 CAPA form

CA/PA #:	-	Revision #:	-
☐ C	☐ CA	☐ PA	

Initiation/Background Information	
Part Number/Catalog Number/Quality System or other identifier of item reportedly deficient	**Lot Number or Serial Number (if Applicable)**
Details of reason for C/CA/PA	
CA/PA Source Categories	Initial Risk Level
☐ Complaint (Comp. #.) ☐ Management Review Meeting ☐ CA/PA Review Board (CRB) ☐ NCR ☐ CA/PA System Review ☐ Investigation (Inv. #.) ☐ Department Management	Risk Evaluation Number: *(Attach copy of risk assessment)* **R1** ☐ **R2** ☐ **R3** ☐

Initiated by:		**Date:**	

Has a Previous CA/PA been assigned that applies to this subject event? ☐ No ☐ Yes (Previous CA/PA #.)	☐ QA Authorization to close this CA/PA	
	QA	**Date**

CA/PA Review Board (CRB)			
	Name	Dept	
CRB assignment of CA/PA Owner:			

C/CA/PA Plan Development By CA/PA Owner
(attach C/CA/PA Plan)

CA/PA Expected Results by CA/PA Owner

(Attach CA/PA Expected Results)

CA/PA #:	CA/PA -	Revision #:	-

CRB Approval of CA/PA Plan

CA/PA Plan approved by CRB? ☐ **Yes** ☐ **No** (If No, provide valid rationale in comments section, below)

Department Head	*Signature*	*Date*

Comments:

CRB Approval to Proceed With CA/PA? ☐ **Yes** ☐ **No** (If No, provide valid rationale in comments section, below.)

Department Head	*Signature*	*Date*

CA/PA Results by CA/PA Owner

(Attach CA/PA Results)

EC/Risk Update By CA/PA Owner (attach additional pages as necessary)

Evidence verifying Effectiveness Criteria	Risk Evaluation Update of Results
Provide Attachment That Details Evidence of Completion of The Effectiveness Criteria	*(Attach Updated Completed Risk Evaluation Form)* Risk Evaluation Number__________

Were additional hazards or nonconformances introduced as a result of the CA/PA taken?
☐ No ☐ Yes

(If yes, attach documentation detailing steps taken to address additional hazards or nonconformances)

Review and Final Approval

☐ **CA/PA Approved** (CAPA Effective Based on Effectiveness Criteria)
☐ **CA/PA Rejected** (EC Criteria **NOT** met)

Department Head	***Signature***	*Date*

Exhibit 2.2 Corrective action plan

	CORRECTIVE ACTION PLAN

CAPA _yy_xxxxY01

Approved By: (Actual Signature) **Date**_______________

Note: CAPA Plan should contain the following elements:

-Description of the Quality Event

-Results of Risk Analysis (attach Risk Analysis Worksheet)

-Remedial actions/Correction/Removals

-Investigation results

-Explanation of why the CA/PA will address the identified events

-Effectiveness Check criteria and due date (to be inserted as a step in the description of the activities)

Exhibit 2.3 Description of the activities

Step	Action: correction/ CA/PA	Implementation team members	Estimated completion date	Actual completion date
1				
2				

Exhibit 2.4 Updated corrective action plan

	CORRECTIVE ACTION PLAN

CAPA_yy_xxxxY01
(revised the yyyy-mm-dd)

Approved By: (Actual Signature) **Date**_______________

Note: CAPA Plan should contain the following elements:

-Description of the Quality Event

-Results of Risk Analysis (attach Risk Analysis Worksheet)

-Remedial actions/Correction/Removals

-Investigation results

-Explanation of why the CA/PA will address the identified events

-Effectiveness Check criteria and due date (to be inserted as a step in the description of the activities)

-…………………

Exhibit 2.5 Description of the activities

Step	Action	CA/PA implementation team members	Estimated completion date	Actual completion date
1				
2				

Exhibit 2.6 CAPA status review

	CAPA SYSTEM REVIEW

MONTH:______________________________

ISSUES DISCUSSED		
DESCRIPTION	**STATUS/ACTION**	**ATTACHMENTS**
1) CAPA REVIEW		
2) CAPA completed		
3) CAPA to be opened		

CAPA SYSTEM REVIEW

SUPPORTING DOCUMENTATION:

- ❑ Complaints, MDR, MDV, and other vigilance reports
- ❑ Service reports
- ❑ QC Hold
- ❑ Corrections/removals
- ❑ Nonconformance control
- ❑ Audits (internal/external)
- ❑ Supplier audits
- ❑ deviations and/or concessions
- ❑ Investigations
- ❑ Training
- ❑ Incoming inspection
- ❑ In process inspection
- ❑ Final product inspection
- ❑ Process control and monitoring
- ❑ Environmental control
- ❑ Maintenance
- ❑ Calibration
- ❑ Validation
- ❑ Change control
- ❑ Product design (design transfer)
- ❑ Productions trends/data: (e.g., Process scrap, rework)
- ❑ Management review meetings
- ❑ Other…..

	CAPA SYSTEM REVIEW
Minute of the meeting :	

Attendants:

CAPA Review Board

QA _____________________________ Date________________

RA ____________________________ Date________________

R&D____________________________ Date________________

Department Head

_____________________________ Date________________

VERIFIED BY CAPA Coordinator:
(DATE AND SIGNATURE)

The nine-step CAPA program

3

Although addressing quality systems and product problems is the company's responsibility, the FDA will not dictate the degree of action that should be taken to address a quality problem, but they do expect companies to have plans in place to keep quality systems and product problems from recurring. The FDA expects companies to address how they will perform their investigations, how they will determine probable root causes, and how they will implement corrective actions. What is more important, the FDA will follow up to see that the plans that are in place are effective.

Corrective action is a reactive tool for system improvement to ensure that significant problems do not recur. Both quality systems and the current good manufacturing practice (CGMP) regulations emphasize corrective actions.

Quality systems approaches call for procedures to be developed and documented *to ensure that the need for action is evaluated relevant to the possible consequences, the root cause of the problem is investigated, possible actions are determined, a selected action is taken within a defined timeframe, and the effectiveness of the action taken is evaluated*.

To establish an effective CAPA program, the nine steps outlined next can be implemented to effectively address any quality systems and product problems.

The nine-step process

- Step 1: Identification of the problem: writing a clear problem statement that includes the what, the where, the when, the who, the how, and how many
- Step 2: Risk/impact assessment determining the risk to the users, products, process
- Step 3: Evaluation of the problem—initiate remedial actions (corrections): what needs to be done to correct the nonconforming issue (segregation, sort, rework, correction, removals)
- Step 4: Data gathering and analysis: looking at data to determine past occurrences of the issue, related investigations, time frames of occurrence, etc.
- Step 5: Investigation: collecting relevant data, investigating all possible causes, and using the information available to determine the cause of the problem
- Step 6: Performing root cause analysis: identifying the factor that, when you fix it, the problem goes away and does not come back. Root Cause Analysis is a systematic approach to get to the true root causes of our process problems
- Step 7: Develop corrective action and preventive action plans: identify action plans per identified root cause
- Step 8: Implement and follow up on action plans: link and confirm that plans were implemented and the linkage to change control
- Step 9: Verify effectiveness—short term and long term: ensuring that the actions taken were effective. A thorough evaluation must be done to make sure that the root cause of the problem has been solved, and that adequate monitoring of the situation is in place

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An appropriate CAPA program

The FDA reported in 2006 that many companies do not employ effective CAPA systems. Typically, the FDA sees 30% to 50% nonconformance in any given Warning Letter. These are generally CAPA-related issues. In one of their meetings, the FDA noted that 76% of all Warning Letters for 2004 had CAPA-related issues. That is an overwhelming percentage, and it occurred because these companies did not do a good enough job not only of identifying corrective and preventive actions but also of validating the effectiveness of their plans. They did not verify that the corrective actions they employed were actually effective. Today, the number one quality system cited in an FDA 483 and warning letter is related to CAPA, and complaints.

A compliant CAPA system should include:

- Preventive action program
- Tie-in design control procedures
- Tie-in process control procedures
- Tie-in risk analysis (Failure Mode and Effect Criticality Analysis (FMECA), FTA, etc.)

Corrective and preventative action procedures require analyzing processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned products, and other sources of *quality data to identify existing and potential causes of nonconforming products, or other quality problems*.

Importance of continuous improvement

One of the most important objectives is to get the quality department to support continuous improvement, which is another thing the FDA and the ISO auditor will be looking for. As you perform the risk analysis, prioritize according to the impact of each item. Select those issues to work on first that have major impact on products or patients. Within the CAPA program, CAPA will not be effective unless you have a solid root cause analysis program. You need to understand and identify those causes. It may be more than one cause that produced the problem. Once you have identified those things, you can analyze and you can appropriately determine what the corrective actions should be.

Another major issue from a regulatory perspective is that we should be learning from the CAPA issues that arise. We should be learning from our mistakes. We should be using those things that continuously failed and that were monitored to see whether there was a trend. Then we should follow through to see if we have actually improved a process or procedure as the result of doing a review or if we are using a Band-Aid approach type system.

Procedural essentials

The FDA will be looking to see how we collect information, how we analyze information, how we identify what we are going to look at, how we identify when we will be investigating or not, and the kinds of quality problems we plan to look at. They will investigate whether we are looking at all the quality inputs we are supposed to be looking at. All our discoveries should be documented. The FDA will be looking at our procedures to discover whether we have objective evidence to show that the system is working; that we are, in fact, identifying the recurring issues from a practical perspective; and that from a reactive perspective, we have identified the corrective actions.

Why include risk analysis in CAPA programs?

The FDA agrees that 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.

Risk-based decision-making

We should also look at the risk-based approach to CAPA. Issues in the quality system must be evaluated from an impact perspective, from a risk-based approach. Analyze the high-risk items before we begin working on the low-risk items, because of the impact they may have on the product or on patients.

A risk-based approach will give a sense of order—a method of prioritization—to the way in which you handle issues. This is especially helpful if there is a high-risk item, specifically because you may have product, process, or patient-related criticality. Examine the system through internal auditing to understand whether the system is working or not.

Exhibit 3.1 Three major concepts

Correction	Corrective action	Preventive action
Correction refers to repair, rework, or adjustment and relates to the disposition of an *existing nonconformity*.	Corrective action relates to the *elimination* of the causes of nonconformity defect, or other undesirable situation in order to prevent *recurrence*.	Preventive action is taken to eliminate the cause of a *potential* nonconformity, defect, or other undesirable situation, in order to prevent *occurrence*.

As observed from inspections on the pharmaceutical and on the device side, the FDA typically categorizes the CAPA system into three concepts systems: (1) remedial corrections, (2) corrective actions, and (3) preventive actions. The first item, remedial corrections, prevents the problem from getting bigger.

The root cause analysis determines what went wrong in the system. The investigation determines the cause or causes so that corrective actions can be implemented to effectively prevent recurrence. Root cause analysis and the identification of corrective action to prevent recurrence are for corrective action. From a preventive action standpoint, you must consider taking corrective action and implementing it in other systems where problems have not yet occurred, so that you can prevent those problems from ever occurring—thus preventing that initial occurrence.

That is the difference between corrective and preventive action. Corrective action deals with preventing recurrence of the event or something that has already failed. Preventive action deals with averting an initial occurrence. Things have not failed yet. You are thus being proactive and taking steps to avoid possible future failure.

In looking at preventive action, we want to make sure that our dealings remain proactive. Preventive action is focusing on things that have not yet failed; it is planning and implementing programs for installation in the company that ensure that we identify issues that could become problems, but are not currently in that category.

Programs that we typically have in place from a preventive action perspective include, for example, calibration and preventive maintenance programs. A review of calibration precision could provide a company with data that can be used to determine when a gauge is getting too close to not meeting the precision requirements. Likewise, when you perform preventive maintenance on equipment, you are not waiting for the equipment to fail, you are working on a proactive basis and preventing that equipment from failing before the fact. There are many other things done in a company that are preventive in form and not reactive, training courses, for example. When we first hire people and we train folks, we are not training to prevent them from making a mistake that they previously made, nor do we wish to prevent them from making another mistake, or problem, in production. They have never been in production. We are being proactive.

Exhibit 3.2 shows the sequence of the nine-step process.

Exhibit 3.2 The nine-step process approach

A review of each of those requirements will be completed and a more thorough review will be provided in Chapters 4 through 12.

Step 1: identification of the event and writing a proper problem statement

4

The first thing, of course, would be to identify that there is a problem. Often we see symptoms and we do not stop to acknowledge that there actually is a problem. We first must identify the problem reflected in the symptoms.

Write a detailed problem statement

In order to decide what must be done when solving the problem, it is important to understand the "issue." Take the time to write the issue clearly and concisely.

Use the "Ws" and "Hs"

The problem statement should include where the event happened, what happened, when it happened, who was involved, how many pieces of whatever were involved, and how the event occurred. Doing a thorough job of identifying the problem is step number one.

Step 1: identification of the problem and effective compliance writing

This involves the following considerations:

1. Measures of excellence
2. Writing effective regulatory documents
3. Identification of the problem
4. How to write a complete problem statement
5. Effective data collection
6. Remedial actions
7. Elements of an effective investigation report
8. List the sources of data involved in an investigation process

Corrective and preventive action systems

These should include requirements to ensure:

- Corrective and preventative actions are initiated and completed.
- Issues related to nonconforming product are fed into CAPA and used to identify trends.

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- Use of analytical and statistical tools.
- Negative trends are analyzed.
- Opportunities for preventative actions are identifiable.
- Effectiveness of the CAPA system.

Root cause/CAPA

- In many cases the majority of the time is spent on the investigative facts, and not enough on the root cause. Remember: finding the true root cause is the reason you are doing the investigation!
- ***Be cautious not to cure a symptom instead of the disease***.

Finding the root cause

Most situations that arise within an organizational context have multiple approaches to resolution. These different approaches generally require different levels of resource expenditure to execute, and due to the immediacy that exists in most organizational situations, there is a tendency to opt for the solution that is the most expedient in terms of dealing with the situation.

The typical tendency is generally to treat the symptom. In doing this, the tendency is generally to treat the symptom rather than the underlying fundamental problem that is actually responsible for the situation occurring.

Yet, in taking the most expeditious approach and dealing with the symptom, rather than the cause, what generally happens is that the situation will, in time, return and need to be dealt with again.

The following case scenarios give examples of treating symptoms rather than the underlying fundamental problems.

Scenario 1

The plant manager walked into the plant and found oil on the floor. He called the foreman over and told him to have maintenance clean up the oil. The next day, when the plant manager was in the same area of the plant, he found oil on the floor again, and he subsequently raked the foreman over the coals for not following his directions from the day before. His parting words were to either get the oil cleaned up or he would find someone who would.

Scenario 2

The plant manager walked into the plant and found oil on the floor. He called the foreman over and asked him why there was oil on the floor. The foreman indicated that it was due to a leaky gasket in the pipe joint above. The plant manager then asked when the gasket had been replaced, and the foreman responded that Maintenance had installed four gaskets over the past few weeks and each one seemed to leak.

The foreman also indicated that Maintenance had been talking to Purchasing about the gaskets, because it seemed they were all bad. The plant manager then went to talk with Purchasing about the situation with the gaskets. The purchasing manager indicated that they had in fact received a bad batch of gaskets from the supplier.

The purchasing manager also indicated that they had been trying for the past 2 months to try to get the supplier to make good on the last order of 5000 gaskets that all seemed to be bad. The plant manager then asked the purchasing manager why they had purchased from this supplier if they were so disreputable, and the purchasing manager said because they were the lowest bidder when quotes were received from various suppliers.

The plant manager then asked the purchasing manager why they went with the lowest bidder, and he indicated that was the direction he had received from the VP of Finance. The plant manager then went to talk to the VP of Finance about the situation. When the plant manager asked the VP of Finance why Purchasing had been directed to always take the lowest bidder, the VP of Finance said, "Because you indicated that we had to be as cost conscious as possible, and purchasing from the lowest bidder saves us lots of money." The plant manager was horrified when he realized that he was the reason there was oil on the plant floor. Bingo!

To find root causes, there is really only one question that is relevant: *What can we learn from this situation*?

Consider scenario 2

- You may find scenario 2 somewhat funny, and laugh at the situation. It would be better if the situation made you weep, because it is often all so true in numerous variations on the same theme.
- Everyone in the organization was doing their best to do the right thing, yet everything ended up screwed up. The root cause of this whole situation is local optimization with no global thought involved.
- Scenario 2 also provides a good example of how one should proceed to do root cause analysis.
- One simply has to continue to ask "Why?" until the pattern is completed and the cause of the difficulty in the situation becomes rather obvious.

However, if we stop to look at root cause analysis tools such as the Five Whys, we can see the benefits of the Five Whys because this type of tool could help to:

- Identify the *root cause* of a problem.
- Determine the relationship between different root causes of a problem.

The Five Whys are one of the simplest tools, and easy to complete without statistical analysis.

Root cause analysis: methods, whys, and the fishbone diagram

The Five Whys can be used individually or as a part of the *fishbone (also known as the cause and effect or Ishikawa) diagram*. The fishbone diagram helps you explore all potential or real causes that result in a single defect or failure. Once all inputs are established on the fishbone, you can use the Five Whys technique to drill down to the root causes.

Understanding the problem statement and the evaluation of the event

What is an evaluation?

An evaluation involves gathering information and reviewing the facts surrounding an event to understand the problem. An evaluation can be used to determine the need for further in-depth investigation. Review the event and the circumstances surrounding the event, and document relevant details, as part of the nonconformance or deviation report.

Seeking quality data

- Solicit feedback to support continuous improvement.
- Customer feedback.
- Employee feedback.

Document the problem

- Establish a priority system.
- Consider impact/risks and select items with major impact.
- Proceed to items with less impact.

Explanation of the problem

- A complete description of the problem must be written.
- The description should be concise but must contain sufficient information to assure that the problem can be easily understood from reading the explanation.

Evidence

- List the specific information available that demonstrates that the problem does exist.
- For example, the evidence for a product defect may be a high percentage of service requests or product returns.
- The evidence for a potential equipment problem may be steadily increasing downtime.

Evaluation

- The situation that has been described and documented in the "Identification" section should now be evaluated to determine, first, the need for action, and then the level of action required.
- The potential impact of the problem and the actual risks to the company and/or customers must be determined.
- Essentially, the reasons that this problem is a concern must be documented.

More on report writing

The first step is being able to clearly describe and discuss the problem. Sometimes what is initially deemed a problem is actually a "symptom" of a greater problem. Major communication may be necessary in order to assess potential problems, and good documentation of the event is critical. Remember, "If it isn't written down, it didn't happen."

Documentation from the initial description of the failure event is the objective. It helps to achieve business objectives such as the following:

- Assists in process improvement initiatives.
- Reasons for documentation in G×P records.
- Completeness and proper documentation of required information in the record is critical.
- Government requirements, e.g., Code of Federal Regulations (CFR).
- Assists in identifying adverse trends.
- Helps to provide rationale for process controls.

Write the Introduction and Purpose of the report. Write appropriately for your audience (inspector/auditor, nonscientific reader). Make sure that you clearly convey the facts of the incident, and always make sure that the documentation is fact-based.

The following are examples of problem statements that attempt to explain the failure. In most cases there is not enough information, therefore making it impossible for the investigation team to properly conduct a true root cause analysis.

Problem statement 1

Quantity affected: 277 trays
Commercial/noncommercial: commercial product
Problem description/problem statement: tray labels with incorrect expiration date printed.

Problem statement 2

Describe event or problem: A QA AQL failure occurred during a QA sampling on shipper #1.

It was noticed that the trays inspected had the label with the incorrect expiration date.

Problem statement 3

Problem description/problem statement: QA failure due to finding of a tray with compromised seal integrity.

Problem statement 4

During QA AQL sampling of shipper 75, a tray with tray seal integrity compromised (one pouched unit in tray seal) was found.

Documentation of the event must include minimum documentation guidelines and describe how to capture the data needed to clearly document a problem statement, provide a clear approach, determine what to include and what not to include in the text, *incorporate relevant attachments, and assess* whether or not other systems are affected by the failure.

Problem statements should cover the Who, What, When, Where, Why, and How of the situation, and in some cases the number of product affected. This should be written such that the person can reconstruct the situation. For example, problem statement A, which follows, lacks information such as where (which equipment number, which lab), who discovered the issue, what was the actual failure, and when was this discovered (date). In contrast, problem statement B includes the who, what, when, where, why, and how.

Problem statement A

The HPLC malfunctioned and therefore the data were not accurate.

VERSUS….

Problem statement B

At approximately 13:30 on April 1, 2014, analyst #123 in the stability release laboratory noticed that the chromatogram for product X lot Y displayed no trace above baseline per test method number 234. As she inspected the equipment, an Agilent HPLC (equipment number 1234), she noticed what seemed to be a failure of the tubing at the point of the sample inlet pump.

Balancing enough information versus too much information

Investigation facts and results must be documented. However, it is possible to give too much information, as shown in problem statement C (in the italicized places).

Problem statement C

At approximately 13:30 on April 1, 2015, analyst #123 in the stability release laboratory, ***who had been working there for many years and was quite diligent***, noticed that the chromatogram for product X lot Y displayed no trace above baseline, which

she really thought was unusual. As she inspected the equipment, she looked at each piece carefully ***as she likes to do in these cases***, and on an Agilent HPLC (equipment number 1234) she noticed what seemed to be a failure of the tubing at the point of the sample inlet pump.

Summary

A proper problem statement will outline the basic facts of the problem: What happened, when it happened, where it happened, who discovered or reported the event, how the event was discovered, and how many/how much/how big the scope of the problem is. The problem statement will also explain why the problem matters. Writing a problem statement is essential because it can help you focus your investigation and create a more cohesive and guided investigation.

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Step 2: risk assessment and impact assessment

5

Part of the evaluation of a failure event is a specific explanation of why the problem is a concern, in terms of the impact of the issue and the risk to the process, products, and patient. This may include the possible impact that the problem may have in terms of costs, function, product quality, safety, reliability, and customer satisfaction.

Why include risk analysis in CAPA programs?

The FDA has written a section to require investigation of the cause of nonconformities relating to process, product, and the quality system, consistent with ISO 9001:1994, Section 4.14.2(b); this requires that nonconforming product discovered before or after distribution be investigated to the degree commensurate with the significance and risk of the nonconformity.

At times a very in-depth investigation will be necessary, while at other times a simple investigation, followed by trend analysis or other appropriate tools, will be acceptable.

Assessing consequences includes using the manufacturer's risk-assessment model to address risks, developing a strategy by deciding which options to implement, taking actions to implement the strategy, and evaluating the results.

Since risk assessment is a reiterative process, the assessment should be repeated if new information is developed that changes the need for, or nature of, risk management. This is also a requirement of ISO14971: Medical devices—Application of risk management to medical devices.

What it means to integrate risk analysis into CAPA

The principles of risk analysis are applied to quality-related events to determine the need for investigation, the scope of investigations and corrective/preventive actions, and the prioritization of investigation and corrective/preventive actions. In a manufacturing quality systems environment, risk assessment is used as a tool in the development of product specifications and critical process parameters. Used in conjunction with process understanding, risk assessment helps manage and control change.

As a result, the risk level provides guidance for the scope and extent of investigation and/or corrective action necessary. Risk level helps provide rationale for decisions relative to the extent of investigation and corrective/preventive action.

Integrating risk analysis into CAPA programs *helps management to put resources where they will add the most value and have the biggest impact on quality*.

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Evaluation

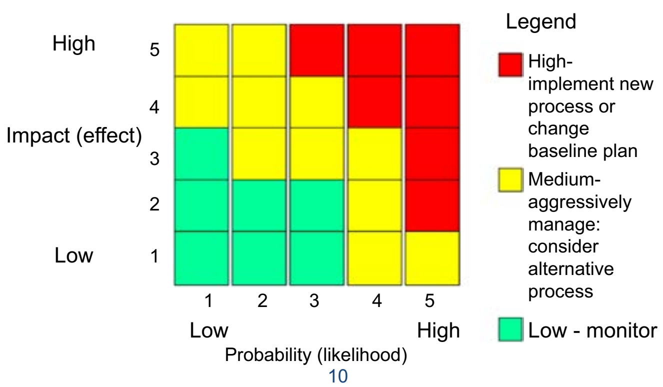
Use risk value to help determine the need for in-depth investigation and corrective or preventive action.

- The situation that has been described and documented in the "identification" section should be evaluated to determine, first, the need for action, and then the level of action required.
- *The potential impact of the problem and the actual risks to the patient, user, company, and/or customers must be determined.*
- Essentially, the reasons that the problem is a concern must be documented.

Potential impact

- This includes the determination of the correction and removal.
- Part of the evaluation is a specific explanation of why the problem is a concern.
- This may include the possible impact that the problem may have in terms of costs, function, product quality, safety, reliability, and customer satisfaction.

Exhibit 5.1 Probability-impact grid



Examples of Severity that may be used to determine a Risk level

1 = Negligible: No injury; potential or minor nuisance.
2 = Marginal: No injury; potential irritation or minor patient discomfort.
3 = Moderate: Degraded product function with the potential for delay in treatment, decline in efficacy, or minor injury.
4 = Major: High degree of product function degradation with the potential for moderate injury or significant decline in efficacy.
5 = Critical: High degree of product function degradation or potential for serious injury or death.

Occurrence

1 = Extremely unlikely: Estimated probability rate less than 1 in 1 million units sold.
2 = Remote: Estimated probability rate less than 1 in 10,000 units sold.
3 = Occasional: Estimated probability rate less than 1 in 1000 units sold.
4 = Probable: Estimated probability rate less than 1 in 100 units sold.
5 = Frequent: Likely throughout the product life cycle.

Assessment of risk

- Using the result of the impact evaluation, the seriousness of the problem is assessed.
- The level of risk that is associated with the problem may affect the actions that are taken.
- For example, a problem that presents a serious risk to the function or safety of a product may be assigned a high priority and require immediate remedial action.
- On the other hand, an observation that a particular machine is experiencing an increasing level of downtime each month may have a lower priority.

Remedial action

- Based on the outcome of the impact and risk evaluations above, it may be determined that immediate remedial action is required to remedy the situation until a thorough investigation and a permanent solution is implemented.
- ***If remedial actions are necessary, the actions and the resources required must be described and documented. The steps that must be taken immediately to avoid any further adverse effects are explained***.
- In some instances, it may be determined that the remedial action is all that is needed. In that case, a rationale is written for that decision, and appropriate follow-up is done.

Failure modes effects analysis and the linkage to preventive action

Failure modes effects analysis (FMEA) is a specific, quantitative process that *identifies risks, evaluates their potential impact, and tracks risk reduction in cases when it is necessary* to diminish an unacceptably high risk level.

Risk-management process

The risk-management process is a living process, whose documents are intended to be maintained throughout design and development and the product life cycle. Risk management is a process consisting of well-defined steps that, when taken in sequence, support better decision-making by contributing to a greater insight into risks and their impacts. It includes elements such as risk identification, assessment, mitigation, elimination, and communication.

The risk-management process should include the following elements:

- Risk analysis
- Risk evaluation
- Risk control
- Production and post production information

What is risk?

- Risk: The probable rate of occurrence of a hazard causing harm *and* the degree of severity of the harm.
  - Harm: Physical injury and/or damage to health or property.
  - Hazard: A potential source of harm to the patient as a result of using the product.

Risk analysis comprises two steps.

- Identification of hazards
- Estimation of the risks for each hazardous event

Risk-management examples

Probability-impact approach

1. Assess importance/severity of the risk.
2. Plot each risk on a probability-impact (P-I) grid (Please refer to exhibit 5.1).
3. Develop a prioritized ranking of risks based on potential effects on project objectives.
4. Set thresholds for identified risks that will initiate risk-response actions.
5. Record risks in a risk-management log/register.

Failure Mode and Effects Analysis—"Bottom Up Approach"

FMEA should be used for a "bottom-up" approach for the first release of the product. FMEA is a structured method to study a design or a process that seeks to anticipate and minimize unwanted design and process failures. It seeks to eliminate or reduce the occurrence of potential failure modes by allocating appropriate mitigating efforts. Risk estimation is determined by rating the severity of each failure mode's effect, and the likelihood of the failure mode occurring and leading to the associated effect.

The level of investigations, and the extent of corrective and preventive actions

This chapter is meant to provide the reader with a step-by-step process for how to perform risk analyses as a means of indicating the ***level of investigations and the***

extent of corrective and preventive actions. Risk analysis also helps to identify the significance and extent of the impact of an event prior to investigation, implementation of corrective/preventive action, and completion of the effectiveness check.

The examples provided in this chapter can be applied to several events and nonconformances, such as product nonconformances, manufacturing deviations, complaints, documentation errors, and other quality system nonconformances that have been determined to require investigation from the CAPA program, management review, or nonconformance control system.

In most companies, quality review board (QRB) members must be appointed by the executive management and represent quality assurance (QA) and/or quality control (QC), manufacturing (Mfg), engineering (R&D), and regulatory affairs (RA). QRB has the responsibility for:

- Reviewing and approving Non Conforming Reports (NCRs) dispositioned as “re-grade” for all risk levels of R1 and R2, or that could be elevated due to the inability to reach consensus by first-level approvers. “Use as is” dispositions are typically not allowed for NCRs with a risk level of R1 or R2.
- Reviewing and approving investigation plans, investigation results, and risk analyses.
- Approving corrective/preventive action plans.
- Prioritizing the implementation of the corrective/preventive actions.
- Monitoring corrective/preventive action progress, including effectiveness.
- Assigning resources for investigations, corrective action, and preventive action execution.
- Initiating corrective and preventive actions (CARs) and assigning them to functional departments or individuals, as they deem necessary.
- Assigning investigations, as required.
- Confirming CARs were implemented and effective.
- Conducting a systematic review of the CAPA system.

Some important definitions related to risk

Risk: Probable rate of occurrence of a hazard causing harm and the degree of severity of the harm.
Risk = Hazard (Severity + probability)

Risk analysis: Investigation of available information to identify hazards and to estimate risks.

Root cause: That most basic reason for an undesirable condition or problem that, if eliminated or corrected, would have prevented it from existing or occurring.

Serious injury: An injury or illness that is life-threatening, results in permanent impairment of a body function or permanent damage to body structure, or necessitates medical or surgical intervention to preclude permanent damage of a body function or permanent damage to a body structure.

Severity: The degree of patient harm or the loss of device efficacy caused by failure.

Severity levels can be defined as follows:

1 = *Critical*	Potential for patient death.
2 = *Major*	Potential for serious injury or requires medical/surgical intervention to prevent possible serious injury.
3 = *Minor*	Potential for minor injury or requires unanticipated surgical/medical intervention to prevent possible minor injury.
4 = *Negligible*	No potential patient injury.

In order to determine the risk level, you will need to perform the following steps:

- First, there needs to be a description of the event, the primary event. This should be documented in a Risk Analysis form (RA form). (Include how the event was discovered and the facts surrounding the event.)
- Identify the category of the primary event from the RA form event categories.
- List the actual failure effects associated with the primary event on the RA form for mislabeled tools, tools with improper labeling could be shipped to a customer.)
- List the potential clinical effects of the primary event on the worksheet (e.g., for mislabeled tools, if the tool were used in surgery the effect would be…). The clinical effects are based on if the product, regardless of QC inspection, were to be used by the customer. The only time this rationale would not be considered is where the product would not be able to pass a QC inspection because the product would not be able to be assembled.
- Severity rating rationale: While considering the actual failure effects and the potential clinical effects, document the severity rationale on the worksheet.
- Identify the potential event causes for the primary event (e.g., based on the information known, specify what might have caused this event to occur).
- Use Exhibit 5.2 as a reference to help complete the severity rating for the identified event category. Document the severity rating on the worksheet.

Exhibit 5.2 Severity ratings for event categories

	Severity rating			
Event categories	**Severity 1 (critical)**	**Severity 2 (major)**	**Severity 3 (minor)**	**Severity 4 (negligible)**
Supplier/procurement process	Event caused by supplier's inability to produce product that meets critical requirements.	Event caused by supplier's inability to produce product that meets major requirements; increased inspectional activities may be necessary.	Event caused by supplier's inability to produce product that meets minor requirements.	Negligible effect by supplier's ability to produce product. *Example*: Cosmetic defect that does not affect functionality.

Exhibit 5.2 Severity ratings for event categories—Cont'd

Event categories	Severity rating Severity 1 (critical)	Severity 2 (major)	Severity 3 (minor)	Severity 4 (negligible)
Distribution and shipping	A distribution system error that would be associated with a failure mode of severity 1.	A distribution system error that would be associated with a failure mode of severity 2. *Example*: Packing configuration not followed, allowing damage to devices where device does not meet a major requirement such as tearing/damaging sterile package.	A distribution system error that would be associated with a failure mode of severity 3. *Example*: Oiler is not packaged appropriately to allow drip rate adjustment knob to allow oil delivery to exceed lube seal capacity.	Distribution and shipping error meets severity level 4.
Acceptance activities	A critical requirement not inspected, and contributed to a *critical* event, or requirement inspected, failure not initially detected and contributed to *critical* event.	Requirement not inspected, and contributed to *major* event or requirement inspected, failure not initially detected and contributed to *major* event. *Example*: The footed-attachment gap not inspected or detected and was out of spec.	Requirement not inspected, and contributed to *minor* event or requirement inspected, failure not initially detected and contributed to *minor* event. *Example*: The nose flow not inspected or detected and was out of spec.	Requirement not inspected, and contributed to *negligible* event or requirement inspected, failure not initially detected and contributed to *negligible* event.

Continued

Exhibit 5.2 Severity ratings for event categories—Cont'd

	Severity rating			
Event categories	**Severity 1 (critical)**	**Severity 2 (major)**	**Severity 3 (minor)**	**Severity 4 (negligible)**
Quality system documentation (Standard operating procedures (SOPs), routers, work instructions, risk analysis forms)	*Critical* information not included or incorrect on required quality system documentation, which could lead to failure of a critical device requirement. *Example*: Complaint involving death received and not documented.	*Major* information not included or incorrect as required by quality system documentation, which could have led to a failure of a major device requirement. *Example*: A complaint associated with a tool head falling into wound site and not being documented. Or a brazed tool routed to grinding without the required torque test being documented.	*Minor* information not included or incorrect as required by quality system documentation, which could have led to a failure of a minor device requirement. *Example*: Finished device testing was not documented on router.	*Negligible* information not included or incorrect as required by quality system documentation, which could have led to a failure of a negligible device requirement.

Identify the frequency of occurrence rationale for the primary event, and determine the frequency of occurrence or possibility of recurrence (*in the absence of any corrective action*).

Exhibit 5.3 Probability of occurrence

Probability of occurrence	**Description**
Frequent	Has occurred often in the past and is likely to continue to occur. Data indicate a >5% failure rate (statistical analysis may be used to support the probability).

Exhibit 5.3 Probability of occurrence—Cont'd

Probability of occurrence	Description
Occasional	Has occurred occasionally and has the potential to recur. Data indicate a 1–5% failure rate (statistical analysis may be used to support the probability).
Remote	Has occurred a few times and has the potential to recur. Data indicate a <1% failure rate (statistical analysis may be used to support the probability).
Improbable	Has occurred once, there is no record of multiple occurrences, and is not expected to recur.

Exhibit 5.4 Severity by probability

Probability	Severity 1	Severity 2	Severity 3	Severity 4
Frequent	R1	R1	R2	R3
Occasional	R1	R2	R3	R4
Remote	R2	R3	R4	R4
Improbable	R3	R3	R4	R4

Determine and perform the evaluation and recommended investigative actions by following Exhibit 5.5. All risk analyses should require the approval of the members of the QRB/top management (formal meeting not required).

Maintenance of risk-analysis results/worksheets/forms

All risk level R1 and R2 NCR/RA form relationships should be reviewed by the QRB/top management on a quarterly basis. All risk level R3 and R4 NCR/RA form relationships should be reviewed by the QRB/top management on a semi annual basis. These reviews should be performed to ensure accuracy of risk levels and will be updated according to the company's risk-management procedures; for example, if the frequency of NCRs against a specific acceptable level increases, then the RA form should be updated to reflect the new risk level, e.g., changing R3 to R2.

Exhibit 5.5 Investigative/corrective actions by risk level

Risk level	Investigation/corrective action acceptability
R1	Intolerable. Risk is unacceptable and must be reduced through extensive corrective action activity. Full evaluation and investigation must be conducted to a depth sufficient to attempt to determine root cause to implement full corrective action. Field correction: If through the course of the evaluation, risk analysis, or investigation, a recall is determined to be required, then it is classified as a Class 1 recall.
R2	Risk is unacceptable and should be reduced as low as reasonably practicable; technical practicability is balanced against risks/benefits. Risk is reduced through extensive effort with substantial corrective action activity. Evaluation must be conducted. Investigations must be performed to determine appropriate mitigation activities (e.g., redesign of product or manufacturing process to improve product quality, labeling modifications to clarify usage because redesigning product is not feasible, modify/improve test methods to improve nonconformance detectability, increased inspection activities to cull out nonconformances). Field correction: If through the course of the evaluation, risk analysis, or investigation, a recall is determined to be required, then it is classified as a Class 2 recall.
R3	Risk is marginally acceptable. Technical and economic factors are balanced against risks/benefits. Risk may be reduced through reasonable corrective action activity. Evaluation must be performed. Results of the evaluation along with any other available information, such as available statistical information, will be used to determine if an investigation is required. Field correction: If through the course of the evaluation, risk analysis, or investigation a recall is determined to be required, then it is classified as a Class 3 recall.
R4	Evaluation is performed. The event is generally acceptable. Further risk reduction, via an investigation and/or corrective action activity, is based upon the discretion of the company. Include data in appropriate quality system and CAPA databases. (Note: All complaints must be evaluated.) Field correction: For risks not affecting patient safety, no recall is warranted.

Note: The risk levels of R1, R2, R3, and R4 are also used to guide the timeliness for completing the evaluations, investigations, and corrective action plans.

Summary

Risk management is one of the most valuable tools that management can use, not only to assess the risk level of an issue but also to determine the level of investigation. It also makes it possible for management to prioritize encountered complaints, CAPAs, deviations, nonconfomances, corrections, and removals.

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Step 3: evaluate event and initiate remedial actions (correction)

6

Part I. Internal corrections

Based on the outcome of the impact and risk evaluations, it may be determined that immediate remedial action is required to remedy the situation until a thorough investigation is performed and a permanent solution is implemented. If remedial actions are necessary, the actions and the resources required are listed. The steps that must be taken immediately to avoid any further adverse effects are explained. The actions that are taken are documented.

In some instances it may be determined that the remedial action is all that is needed. In that case, a rationale is written for that decision, and appropriate follow-up is done.

Investigation

In this step of the process, a procedure is written for conducting an investigation into the problem.

- A written plan helps assure that the investigation is complete and nothing is missed.
- The procedure should include an objective for the actions that will be taken, the procedure to be followed, the personnel who will be responsible, and any other anticipated resources needed.

In many cases, companies identify nonconforming products before they are shipped. A nonconformity or suspect product should never be shipped to the customer; however, if this happens, the company has to immediately evaluate the action needed and notify the customer via phone, fax, or e-mail.

Whenever personnel find nonconformities within the receiving, manufacturing, or storage areas they must take appropriate steps so that the parts, products, drugs, etc., are identified and segregated from production by completing a "Hold—Do Not Process" tag. The originator should complete the item number, description, purchase/shop order number, quantity, and reason for rejection or nonconformance. The originator can then sign and date the tag and should affix that tag to the part(s) affected. The supervisor of quality assurance can then review to determine if the part or assembly should be scrapped, can be reworked to a conforming condition, or can be used.

CAPA in the Pharmaceutical and Biotech Industries. http://dx.doi.org/10.1016/B978-1-907568-58-9.00006-0

Procedures for the conditions mentioned

If the part or assembly cannot be reworked, and must be scrapped, the supervisor should mark “Scrap” on the “Hold—Do Not Process” tag. The parts affected will be scrapped.

If the nonconforming part(s) can be reworked to the original engineering specifications, the supervisor should check “Rework” and document the rework instructions on the “Hold—Do Not Process” tag that is accompanying the part(s) and sign and date the tag.

> *Procedures for rework must include retesting and reevaluation of the nonconforming product after rework, to ensure that the product meets its current approved specifications. Rework and reevaluation activities, including a determination of any adverse effect from the rework upon the product, shall be documented in the DHR.*
>
> *Subpart I–Nonconforming Product: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=820&showFR=1&subpartNode=21:8.0.1.1.12.9.*

As noted in the previous paragraph, procedures for rework must be created, reviewed, and approved prior to the execution of any reworks. Upon completion of the rework, with the part(s) now meeting the original specifications, the “Hold—Do Not Process” tag can be removed from the part(s), and the part(s) or products can be returned to “production ready” status.

Concession to use as is

“Use as is” disposition should be approved by Quality. If the parts have been dispositioned as “Use as is,” or with concession, a “Request for deviation” should be completed. “Use as is” should be marked on the Hold—Do Not Process Tag and the tag will be signed and dated.

The “Hold—Do Not Process” tag will be removed from the part(s). The part(s) can then be returned to “production ready” status. Remember that the reworked products must meet all of the current design and performance standards verified through the current testing procedures and inspection procedures. The rework instructions should be documented in the device history record or the batch history record.

As you start to complete the evaluation of the issue or nonconformance, many of the corrections may include some form of retrospective review of other systems, products, processes, etc. All remedial actions should be documented in the CAPA form under corrections.

Exhibit 6.1 shows examples of several internal corrections, which are linked to each individual root cause that is being addressed.

Exhibit 6.1 CAPA plan

Attachment 9.2 **Page_ of _**		**CAPA PLAN**	
CAPA Data base Event # 1234	**CA / PA(s)#: N/A**	**Revision: 2.0**	**Date:** Jul 12, 2015
Event Owner:	**Jane Smith**	**CA/PA Owner:**	**John Doe**

Root Cause(s) to be addressed:

Root Causes

RC1. Missing other key indicators (SCARs, NCRs, Audit results) taken into consideration during supplier evaluation

RC2. Weak product and materials classification all direct materials defined as critical, without scaling of the criticality level

RC3. Supplier Qualification not taken in account properly—Result of possible audit during supplier qualification process not taken in account as a base for right supplier treatment and evaluation

RC4. No cross-functional team in definition, supplier evaluation defined from one-sided view, only by logistic

RC5. Lack of knowledge and experiences with supplier treatment adjustment

RC6. Not centralized system for appropriate data collection—no local data collection on one place (server) from affected areas (logistic, purchasing, quality) which makes evaluations more appropriate

Contributing Causes

CC1. Primary definition of the supplier evaluation not adequate

CC2. No definition of the scoring vs. exact actions to be performed/taken

CC3. No required timeline for actions to be taken

CC4. Actions defined only in way as optional

Verify or validate the corrections, corrective and preventive action to ensure that such action is effective and does not adversely affect the finished device;

☐ **Correction** ☐ **Corrective Action** ☐ **Preventive Action**

CA/PA Owner Name	**Job Title**	**Signature**	**Date**
Jane Smith	QA Manager		

Actions Required:

☒ **Correction** ☒ **Corrective Action** ☐ **Preventive Action**

Contributors: ☐ *N/A for simple corrective actions*

Name:	**Job Title:**	**Location/Site:**
Jane Smith	QA Manager	Manufacturing
John Doe	Logistic Manager	Manufacturing

Attachment 9.2	*CAPA PLAN*
Page_ of _	

Corrective Action / Preventive Action Plan:					
Root Cause #	**Action/ Task to be Completed:**	**Action Type: (C/CA / PA)**	**Responsibility**	**Target Date for Completion**	**Objective Evidence**
RC1 CC1	Redefine supplier evaluation (G803005), from current process counting only with received value and rejected value to the process which will include amount of the SCARs, NCRs, and also results of the Supplier audits	CA# 1	Jane Smith John Doe		SOP XXX Supplier evaluation new effective version
RC1	In SOP XXX define system of the scoring which will count and give appropriate ranking base on all criteria including new implemented	CA# 2	Jane Smith John Doe		SOP XXX Supplier evaluation new effective version
RC1	Supplier evaluation have to be adjusted on quarter base, to reflect possible negative trends of the supplier	PA #1	Jane Smith John Doe		SOP XXX Supplier evaluation new effective version
CC2 CC4	In supplier evaluation procedure define what exact action to be taken vs. achieved scoring	CA# 3	Jane Smith John Doe		G803005 Supplier evaluation new effective version
CC3	In supplier evaluation procedure (XXX) define required timeline for specific action to be taken after the supplier evaluation	CA #4	Jane Smith John Doe		SOP XXX Supplier evaluation new effective version
RC2	Redefine/readjust criticality level of the component for all direct materials	CA #5	Jane Smith John Doe		SOP XXX Product/service categorization new effective version

Corrective Action / Preventive Action Plan:					
Root Cause #	**Action/ Task to be Completed:**	**Action Type: (C/CA / PA)**	**Responsibility**	**Target Date for Completion**	**Objective Evidence**
RC2	Describe adjustment of the criticality level for new coming components	PA #2	Jane Smith John Doe		SOP XXX Product/service categorization new effective version
RC3	Define exact system how to reflect supplier audit from phase of the supplier qualification to the supplier evaluation	CA #6	Jane Smith John Doe		SOP XXX Supplier evaluation new effective version SOP XXX Supplier qualification new effective version
RC3	SOP for supplier audit revise	CA #7	Jane Smith John Doe		SOP XXX Supplier audit new effective version
RC4	All new definitions to be done with involvement of all departments, cross-functional definition by Logistic, Purchasing, Quality department	CA #8	Jane Smith John Doe		Attendance evidence
RC5	Training for supplier management (e.g., supplier auditing)	CA #9	Jane Smith John Doe		Training records + certificate
RC5	Implement new position SQA (Supplier Quality Assurance)	CA #10	Jane Smith John Doe		Job description and organization chart to contain SQA position
RC6	On local server (O:\ drive) create shared folder between Logistics, Purchasing, and Quality	CA #11	Jane Smith John Doe		Folder map and appropriate templates
RC6	Define exact content and structure of created folder to ensure clear addressing and storing of the relevant data	CA #12	Jane Smith John Doe		Folder map and appropriate templates

Part II. Corrections and removals (external corrections)

Remedial actions are not just related to internal corrections such as reworks and regrades. When an event occurs, the organization should also review the impact upon the user or patient. It is important to define and document a standard operating procedure to establish a process for identifying and assigning responsibilities for field action activities, including field safety corrective actions (FSCAs), and describe the method for conducting corrections, removals, or recalls in accordance with regulatory requirements.

This chapter outlines the means for determining product recall requirements and for recalling distributed product in which an unexpected risk to health has been identified or if a product not recalled would otherwise violate some aspect of the Federal Food, Drug, and Cosmetic Act (Section 519(f)). Exhibit 6.2 can be used to initiate the review of harm to patient or user.

Responsibilities

When it comes to any type of field action, senior management must be involved and should be responsible for approving field action decisions, determining reportability, and for ensuring implementation of this procedure corporate-wide.

In most cases, quality assurance/regulatory affairs (QA/RA) is responsible for implementing the correction and removal process and completing a health hazard evaluation (HHE) form.

Senior facility management should be responsible for providing all qualified personnel, documentation, management, and other resources needed to ensure effective and timely implementation of the correction process.

A facility field action coordinator or designee is typically responsible for:

- Establishing an investigation team (including team members from all facilities affected).
- Conducting HHEs.
- Conducting field actions.
- Notifying companies when the HHE determines that a field action may be required.

Senior facility management should be responsible for providing all qualified personnel, documentation, management, and other resources needed to ensure effective and timely implementation of all actions needed.

General requirements

Field safety corrective actions

The organization's top management should decide whether or not the recall action will be reported as a field safety corrective action to any competent authority, and submit the required reports. The facility field action coordinator or designee should also

Exhibit 6.2 CAPA plan examples of corrections

<table>
<tr><td>FDA – 483 OBSERVATION # 2</td><td>DATE : 7/13/2014</td><td>INVESTIGATION NO: 1

CAPA NO: 1</td></tr>
<tr><td colspan="3">QUALITY SYSTEMS IMPACT ASSESSMENT (PRODUCT, END USER, PROCESS)

Observation 2

Failure to adequately evaluate and select potential suppliers, contractors, and consultants on the basis of their ability to meet specified requirements, including quality requirements and failure to document this evaluation, as required by 21 CFR 820.50(a)(1). For example

Your firm did not adequately identify contractor's qualification requirements.</td></tr>
<tr><td colspan="3">REMEDIAL ACTIONS (CORRECTIONS)

RETROSPECTIVE REVIEW

1. Review Supplier Evaluation procedure to identify review of qualifications and the approval process for contract services
2. Revised Supplier Evaluation procedure to include review of qualifications and the approval process for contract services
3. Review of all suppliers in order to identify which suppliers need to be qualified and approved and/or removed based on new supplier evaluation process (per revised procedure)
4. Update Approved supplier list
5. Update Qualified supplier list
6. Provide approved supplier evaluations for grandfathered suppliers.
7. Provide supplier evaluations for those non-grandfathered suppliers.
8. Retrospective review of other purchasing control requirements to ensure that all QSR requirements are addressed and completed.</td></tr>
<tr><td colspan="3">RISK/IMPACT ASSESSMENT: High/Critical</td></tr>
<tr><td colspan="3">INVESTIGATION PART 1: DATA GATHERING AND DATA ANALYSIS:

• Review of current Purchasing and Supplier Evaluation procedures, processes, and data:
• Review of all contracted services in order to determine which suppliers need to be qualified, approved, and added to the approved supplier list.
• Preform evaluations and approval for contracted service suppliers</td></tr>
</table>

notify the notified body of field safety corrective actions initiated by the company for products distributed in the EEC.

Correction and removals process

The FDA requires that companies have a process in place in the event that any company employee who becomes aware of any information from any source must immediately contact the facility field action coordinator, or designee, if such information:

- Reasonably suggests that a company or device may have caused or contributed to a death or serious adverse health consequences.
- Indicates that the device has malfunctioned and such malfunction likely would result in a death or serious adverse health consequences if it were to recur in the device or a similar company device.
- May suggest that a distributed device does not comply with applicable regulatory or statutory requirements.
- Reasonably suggests that a device distributed by the company poses a risk greater than expected.
- Reasonably suggests that product with incorrect identification has left the manufacturing facility where produced.
- May suggest that product that has been distributed does not conform to product specifications.

The first step is recognizing that an event has occurred. Then a field action coordinator will review the information and complete an HHE to document the decision of whether to initiate a correction or removal.

The completed form should be maintained with the originating complaint, CAPA, nonconformance, etc., file.
A log should be kept for HHEs.

Conducting a health hazard evaluation and determining the health/risk index.

The field action coordinator or designee is typically responsible for obtaining all reasonably available information regarding the event or potential event. The information obtained may include, but not be limited to, the following:

- Name of device and other descriptive information.
- Device lot number, model number, and/or serial number.
- Details regarding the nature of the event or potential event.
- Extent/occurrences of the adverse event.
- Manufacturing, inspection, testing, and raw material records regarding the subject device.
- Detailed device location breakdown, including:
  - Quantity of the device located in premises owned by, or under the control of, the company.
  - Quantity of the device distributed to customers.
- Inspection results of subject device.
- Inspection results by quality assurance department of undistributed inventories, if needed.
- Investigating the root cause of the event.

The factors to be considered in conducting an HHE should include, but should not be limited to, the following:
  - Whether any deaths or serious injuries have already occurred from the use of the device or product.
  - Whether any existing conditions could cause or contribute to a clinical situation that could expose patients or device users to a potential health hazard.
  - An assessment of the actual or potential health hazard to various segments of the population (e.g., children, the elderly, or pregnant women) who are expected to use or be exposed to the device, with particular attention paid to the hazard to those individuals who may be at greater risk.
  - An assessment of the degree of seriousness of the actual or potential health hazard to which the population at risk would be exposed.
  - An assessment of the likelihood of occurrence of the actual or potential health hazard.
  - An assessment of the consequences (immediate and long range) of the occurrence of the potential health hazard.
- Notifying appropriate warehouse/inventory managers, returned product personnel, and other appropriate team members to ensure that product is not further distributed:
  - Electronic inventory controls shall be used where available.
  - The affected local manager(s) are responsible for physically pulling the affected lot(s) from the shelves, ensuring that the product is physically placed in a quarantine area and electronically entering them (subinventory transfer). This prevents picking and shipping of the product.

The field action coordinator should notify the regulatory compliance designee if the information review reasonably suggests that a field action may be appropriate.

Based on the HHE results or other available information, the field action committee will then recommend whether a correction or removal action is indicated and develop an appropriate strategy for such action. If the regulatory compliance designee concurs with the recommendation, it may be initiated.

A field action team should be established at the discretion of senior management. Such correction or removal activity should include:

- Market withdrawal.
- Stock recovery.
- Labeling change, including new instructions.
- Safety alert.
- Field correction or servicing, or recall.
- Corrections or removals should be initiated and completed on a timely basis. Records of such action should be maintained in accordance with the requirements of 21 CFR Part 806 and other applicable regulations.
- Determinations of whether to conduct correction, removal, or recall activities should be documented on the HHE form.

Typically, regulatory affairs or regulatory compliance, based on the outcome of the HHE, will determine the need to notify the appropriate regulatory authorities including, but not limited to, the FDA.

In most instances, at the discretion of Senior Management, the completed HHE and draft notification letter(s) will be forwarded to the FDA district coordinator for review prior to release.

The company should submit reports to the FDA within 10 working days of making the field action decision, and this should be documented on the HHE.

Quality assurance is typically responsible for initiating the appropriate corrective and preventive action according to the organization's corrective and preventive action system SOP.

Process for conducting a correction/removal

A field action coordinator or designee along with related functional group(s) should perform the following steps when conducting a correction or removal:

- Determine the scope of the devices/products/lots affected.
- Quarantine undistributed inventories.
- Identify accounts to which affected product has been distributed.
- Notify affected distributors, sales representatives, company affiliates, and consignees.
- Distributors or sales representatives may be instructed to assist in contacting accounts that have received affected product and assist in the correction/removal and associated effectiveness checks.

During removal actions, the field action coordinator or designee should follow up on removal activities until affected products are retrieved or reconciled. If product is unable to be located, documented evidence of the retrieval efforts must be included in the reconciliation file.

A field action coordinator should place undistributed and recovered product in a designated "quarantine" location to prevent inadvertent use or unauthorized distribution of the product.

The field action coordinator shall retain copies of documents relating to the correction or removal, and the reasons for initiating the activity within the recalls/corrections/removal files. Evaluate effectiveness of correction, removal, or recall.

Recalled/recovered product disposition

A field action coordinator along with quality assurance should remove, collect, and quarantine all in-house and distributed product subject to recall, including product in new product hold (when applicable). Correction, rework, scrapping, or other disposition of removed product should be in accordance with the company's nonconformance SOP.

If the product removal is FDA reportable, disposition of product shall not take place until approval of said actions from the FDA.

Notice of correction, removal, and recall (i.e., field action communication)

Notices of field actions should be issued in a manner such that the format, content, and extent of the notice is commensurate with the hazard, if any, of the product being corrected, removed, or recalled and the strategy developed for that action. In general terms, the purpose of the notice is to convey:

That the product in question is subject to a correction, removal, or recall.

That further distribution or use of any remaining product should cease immediately.

Instructions regarding what to do with the product.

The field action coordinator, when applicable with the support of senior management, should compose the notice of corrections, removals, and recalls. Content of notices of corrections, removals, and recalls should be written in accordance with the following guidelines:

> Correspondence should be conspicuously marked. For example: "Urgent medical device or Drug recall (or removal or correction or field safety notice)."

The correspondence header should clearly identify the product and product description to enable accurate and immediate identification, in addition to notification date. Details on affected devices should be given, which includes specific details to enable the affected product to be easily identified, such as the part number(s), lot number(s), batch numbers and serial numbers.

Description of the problem to include a factual and concise statement explaining the reason for the correction, removal, or recall; including a description of the device malfunction or deficiency; clarification of the potential hazard associated with the continued use of the device; and the associated risk to patient, user, or other person, and possible risk to patients associated with previous use of affected devices.

Advise on actions to be taken by the user, which may include specific instructions on what should be done with the products, recommended patient follow-up, if any, and a request to forward this notification to others if the product has been further distributed.

Provide a designated contact number, address, name of individual at company, and business hours. Provide a ready means for the recipient of the notice to report to company whether the recipient has any product. The notice should not contain irrelevant qualifications, promotional materials, or any other statement that may detract from the message.

Where necessary, follow-up communications should be sent to those who fail to respond to the initial notice.

Notification method

Notices should to be issued to the consignees using traceable methods and carriers. Method of notification used is dependent on the scope and strategy associated with the action. Methods may include electronic mail, facsimile, first-class letters, United Parcel Service, or Federal Express.

FDA reportable field action

If the company determines that a report to the FDA is required, the report should include the following.

In the cover letter (if applicable), include the company's seven-digit FDA registration number; the month, day, and year the report is made; a sequence number; and the report type designation "C" or "R."

- Name, address, and telephone number of the company and the name, title, address, and telephone number of company's field action coordinator or designee.
- The brand name and the common name, classification name, or usual name of the device and the intended use of the device.
- Marketing status of the device, i.e., any applicable premarket notification number, premarket approval number, or indication that the device is a preamendment device, and the device listing number.
- The part number of the device and the manufacturing lot number of the device or other identification number.
- The manufacturer's name, address, and phone number, and contact person if different from that of the person submitting the report.
- A description of the event(s) giving rise to the information reported and the corrective or removal actions that have been, and are expected to be, taken.
- Any reported illness or injury that has occurred with the use of the device. When applicable, include the MDR number(s).
- The total number of devices manufactured or distributed subject to the correction or removal and the number of products subject to the correction or removal.
- The date of manufacture or distribution and the device's expiration date or expected life.
- The names, addresses, and telephone numbers of all domestic and foreign consignees of the device and the dates and number of devices distributed to each consignee.

A copy of all communications regarding the correction or removal and the names and addresses of all recipients of the communications. If any required information is not immediately available, a statement should be included as to why it is not available and when it will be submitted.

Nonreportable field actions

The FDA also requires that records be kept for the corrections and/or removals that are not deemed to be reportable. The records should have:

Brand name
Catalog number
Lot number(s)
Description of events
Justification of why the event is not reportable
Conclusions and follow-ups

Copies of all communications regarding the event should be kept along with the report for the expected life of the device per procedural record retention requirements.

Exhibit 6.3 CAPA risk assessment guide

CAPA Risk Assessment Guide

Date: CAPA#

Subject:____

If there is potential that nonconforming product has been distributed notify the Post Market Regulatory Compliance Manager. **If No**, provide rationale.

HHE number, if initiated? ___________

DFMEA/PFMECA Reviewed? ☐Yes ☐No (Not product related issue)
If Yes, document results below and attach document.
Risk File Requires Update? ☐Yes ☐No If yes, Action Number ____

Patient Severity	**Check Box**
No adverse health outcome.	
Transient, minor impairment or complaints.	
Temporary or reversible impairment (without medical intervention).	
Necessitates minor medical intervention.	
Necessitates surgical intervention.	
Results in permanent impairment of body function or permanent damage to a body structure.	
Life-threatening (death has or could occur).	
Refer to HHE (if created prior to CAPA Request)	

Regulatory Impact	**Rating**	**Check Box**
Issue that is not systemic, or an isolated incident that may be addressed in an informal manner where no field action is required	Minor	
Issue that is deemed to be systemic (widespread) or of a nature to have significant impact on a product, process, or system or where field action is required	Major	

Frequency ☐**Low** ☐**Med** ☐**High**

Describe Business Impact if any: ____

Issue had occurred previously? ☐No ☐Yes…(**if yes**, CA#'s)

☐**Category A** ☐ **Category B**

Category A (considered the highest priority and given the greatest importance)

CAPA Risk Assessment Guide

Date:

CAPA#

Rationale/Recommended Actions to be documented in CAPA Request

____
____
____
____
____
____

Patient Severity Reviewed by: ___________________________
____

Print/Signature/Date: ___________________________
____
____
____

Regulatory Impact Reviewed by: (RA/QA) ___________________________
____

Print/Signature/Date: ___________________________
____

Reviewed for nonconforming product (RA/QA) ___________________________

Print/Signature/Date: ___________________________

☐ ☐

FMEA/PFMECA Reviewed / Not Reviewed by (CAPA Engineer):__________

Print/Signature/Date: ___________________________

CAPA Coordinator ___________________________

Print/Signature/Date: ___________________________

Step 4: data gathering and analysis

7

Potential causes and data collection and analysis

The analysis of data is another very important step since the main goal is to gather previous sources of information for the sake of reviewing if the failure has previously occurred and, of course, to understand if the corrective actions were ineffective since the event may be related to past failures and possible ineffective action. Therefore, the goal of data analysis and data modeling is to identify useful information, which could be used for suggesting conclusions and, more importantly, to supporting decision-making based on factual data sources. This can only be achieved if the organization establishes procedures for collecting the right type of data, for analyzing data, and by identifying up front the techniques for interpreting the results of such procedures.

Data analysis has multiple approaches, and many techniques can be used. Of course, to do this, the organization needs to identify what data is critical to their business or processes, and to assign responsibilities for the ongoing data collection and data analysis. This could be as simple as data collection to maintain histograms over specific periods. By implementing an effective data collection program, whenever data needs to be reviewed during an investigation, the process will be painless and more efficient without the need for additional resources or time.

Data analysis should be planned to include appropriate statistical methodology and should be employed where necessary to detect and address recurring quality problems.

Data, quality indicators, and triggers

The need for correction and corrective actions will be determined when a quality indicator has triggered, where a risk assessment determines that action must be taken, or while conducting a review of each quality indicator's trend during the corrective and preventive action (CAPA) review meeting. In addition, management should also initiate CAPA requests for items they determine significant. The ultimate decision for initiating a CAPA should rest with the senior quality manager.

Levels of reviews

- At the business level, key indicators should be used to determine whether quality objectives are being achieved, and internal audits assess the suitability and effectiveness of the quality management system.
- At the process level, data is analyzed from a specific product, and process-monitoring sources are typically defined in CAPA procedures and/or production and process control procedures.

CAPA in the Pharmaceutical and Biotech Industries. http://dx.doi.org/10.1016/B978-1-907568-58-9.00007-2

- At the workstation level, routine monitoring of key parameters should be planned and implemented as required by an approved control plan, quality plan, or protocol.

Analysis of source quality data will include global analysis across all source CAPA data lines (i.e., analysis of common factors, such as problem, product, lot number, staff, and other criteria against all corresponding source CAPA data, including quality complaints, nonconformances, internal and external audits, and CAPA reports) to identify any additional existing and potential quality problems.

Data collection should be planned as follows

Data owners may report independently within their department or through interface with the Quality Assurance group. The Quality Assurance/Regulatory department is usually responsible for publishing CAPA trigger matrix meeting reports in support of the Quality Scorecard. This effort typically involves direct interface with data owners who may provide data collection requirements and who may provide comments needed for management review of adverse trends. Meetings should be held monthly or quarterly to review quality indicator results with emphasis on areas that fail to achieve targets or that have unfavorable trends.

Data analysis and the investigation process

At the beginning of the investigation, a list of possible causes is created. This will form the basis for collecting relevant information, test data, and provide the investigation owner with information to decide the most appropriate investigation methods to be utilized. For example, consider the situation where a large batch of parts from a monitor final testing phase was discovered to be nonconforming. There are many possible causes for this condition including operator error, incorrect software, an uncalibrated tool, a material problem, or a design problem. By considering possible causes, appropriate information and data can be collected that will ultimately be used to determine the origin of the problem.

Data collection

A data collection program should be established up front, and this program should describe the basis for collecting relevant information, assigned responsibilities for the collection, and ongoing data review and analysis. There are many possible causes for ongoing failure situations including equipment wear and tear, operator error, incorrect software, a dull or broken tool, incorrect or obsolete procedures and drawings, material problems, design problems, off-label use of the product, etc. By considering all possible causes, appropriate information and data can be collected that will be ultimately used to determine the root cause of the problem.

Potential causes and data collection and analysis

Typically at the beginning of the investigation, a list of possible causes is created. This will form the basis for collecting relevant information, testing data, and providing the investigation owner with enough information that could be used to determine recurrence rates.

For example, during a complaint investigation a review of recurrence of the failure should include a time frame. How would you determine the appropriate time frame? You can start by looking at the manufactured dates for the products that had the same or similar type of failures. This will provide a time period.

Results and data

The results of the data collection must be documented and organized. This may include a combination of testing results and/or a review of records, processes, service information, design controls, operations, and any other data that may lead to a determination of the fundamental cause of the problem.

The resulting documentation should be complete and address all of the possible causes that were previously determined. This information is used to determine the root cause of the problem.

Begin by looking at the methods to be used to collect the information. For the CAPA program to work, the data to be analyzed must be appropriate to the system. Ensure that the data is sound, that it is not junk data—and, last year's statistics have limited value for the company. Look at data on a timely basis. Identify who will look at the data, determine how you are going to measure it, and monitor the activities that are going to be used for a CAPA prospective data analysis. Determine when you will perform the analysis or the evaluation of the data collection activities.

One important element within the CAPA program is the collection and analysis of data to identify all the things that could be a potentially nonconforming product issue. For example, let us say we have noticed reworking of procedures or reworking of product. Those are telling quality indicators that we should not ignore. The existence of reworking indicates a quality problem; if you rework, you have a problem. Either you are not manufacturing the way you are supposed to or you are deviating from the process. Under these circumstances, you want to make sure that within the CAPA program you require an investigation.

Gather information and analyze data

Once the problem has been identified, then we start gathering data for the data analysis. This is the beginning of the investigation for the root cause. Data analysis begins by considering what information is needed. We do the analysis and gather the data as interrelated steps. We may go back and forth between the two steps, especially at the beginning, while we are discovering what information is needed. Go back to the well of information until you have everything you feel answers the outstanding questions.

You may be looking at batch records, DHRs, complaints, or service reports. You are gathering the information you need to perform the data analysis, which is the third step in the program. As you are doing the investigation, you must ask the following: what are the procedures or what are the processes involved, what is the equipment, what has changed, and are these correct procedures? Keep asking questions until you have satisfied every open issue to obtain the information you need and have a clear understanding of the event; you may start interrogating people—talking to people who work on the processes or procedures. Keep asking questions to get all the information and documentation you feel is necessary to perform an effective root cause analysis.

Once you have all the data in front of you, even as you are analyzing the data, things may be falling into place. You should be thinking of different ways to look at the data. Try a fault tree analysis, or a fishbone, or other chart types to look at the data in new ways. Each of these tools can help you see the information in a different light.

CAPA system data collection and analysis

The purpose of this section is to outline the requirements for collecting and analyzing data from the CAPA system to achieve consistency in the approach, evaluation, analysis, and reporting of quality data.

The general process for data collection and analysis

Step 1

- Identify proper quality data owners review metrics for CAPA data review meetings and provide an explanation of the data utilizing the appropriate method of analysis. This must be defined in the company's data trends procedure or a corrective and preventive action system data and analysis procedure
- This analysis should include, at minimum, the following:
    - Identification of any known or suspected causes
    - Any additional issues or concerns

Step 2

The data owner should compile the completed metrics in preparation for the CAPA system review meetings.

Step 3

The quality data owners, at the CAPA system review meeting, present quality metrics and analysis.

Step 4

The CAPA Review Board reviews the quality metrics and analysis to determine the need for further action, if required.

Note: Based on further analysis or new information, management should determine that some metrics are no longer useful and replace them with other metrics or alternate methods of analysis. The normal change order process should be followed when changes to this document are made.

CAPA system review

To achieve consistency in the approach, evaluation, analysis, and reporting of quality data, the following is essential and should be documented as appropriate:

- Analysis of the CAPA system is conducted monthly through the CAPA system review meetings. The meetings should be conducted as follows.
- The CAPA coordinator should establish in advance and communicate to all participants the exact dates, time, duration, and location.
- The CAPA coordinator should establish an agenda and prepare and maintain minutes.
- The CAPA coordinator should lead the meeting per the agenda, facilitate discussion, and circulate the attendance sheet to attendees.
- The CAPA coordinator should confirm that the required attendees, or their designees, from each functional area are present.
- Department heads should appoint designees in the event the department head is not able to attend the meeting. The department head should document these designees.
  - No more than two designees are allowed to be in attendance at the CAPA review meeting.
- Acceptable written documentation may include memos, e-mails, etc.
- Presenters from quality data sources and departments present processed data and analysis for review.
- Presenters advise the CAPA System Review Board when additional resources are necessary to complete corrective actions and/or preventive actions.

The CAPA System Review Board should review the following:

- Open action items from the previous meeting to analyze their status and timeliness. This ensures that meetings are closing the loop on assignments made from the previous meetings.
- Review metrics to ensure that investigations and CAPAs are effective and are processed within the timelines established.
- Review metrics for appropriateness and determine if additional metrics or the reporting frequencies of metrics are adequate, if applicable.
- Discuss late/unresolved investigations and CAPAs and decide on further action.
- Identify if new investigations or CAPAs are required and assign them to individuals or functional department(s) with due dates for completion.
- Examples of where additional action is indicated include, but are not limited to, the following:
  - Perceived high risk or indication of high risk is identified through the use of risk management tools.
  - Data presented demonstrates an adverse trend.

- These actions are to be documented in the CAPA system review meeting minutes.
- Determine the appropriateness of the CAPA review meeting frequency.

The CAPA coordinator should document any new action items related to corrective and preventive actions and enter into the CAPA system.

The CAPA coordinator should publish and retain minutes of the meeting. Minutes of the meeting are documented. The minutes should be approved by the CAPA Review Board members that attended the CAPA system review meeting, and they are verified by the CAPA coordinator.

The target date for publication of meeting minutes is 10 business days from the date of the CAPA system review meeting.

The CAPA coordinator should prepare a summary report(s) for management review meetings. This report(s) should include a summary of the statistical reports required by the CAPA system data and analysis procedure.

Problem analysis

The problem analysis is the conclusive interpretation of the data gathered in the previous steps. The analysis tools may vary from general problem-solving techniques to very specific elaboration programs for the determination of the reason behind a problem occurrence.

Analysis of data

Data should be collected and analyzed to demonstrate the suitability and effectiveness of the quality management system and to evaluate where improvements can be made. Data sources include but are not limited to the following:

- Feedback
- Nonconformance data
- Supplier data
- CAPA trends
- Test results
- Management review process
- Internal auditing

Improvement

The quality improvement process should be established based on data trends. This will help a company to achieve the organization's continuous improvement of culture and values and improvement of setting goals and objectives.

Investigation process metrics

- Metrics collected from the investigation process are identified in the CAPA System Data and Analysis Procedure TP0398.
- The CAPA coordinator (or designee) is responsible to produce reports that contain metrics and analysis that determine if further action is required as defined in the company's Corrective and Preventive Action System Data and Analysis process.

Closed loop corrective action

- Investigation data is analyzed and forwarded to the CAPA system review meetings. The results of this analysis and any further decision to take action are recorded in the meeting minutes from the CAPA system review meetings.
- Items requiring further action are elevated to the management review.

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Step 5: investigation

8

When investigation is needed

Investigations should be generally carried out when failures occur and, in some cases, when recurring deviations occur. There are cases when investigations occur where no (true) deviation has occurred, for example, out of trend or yields creeping up or down. Investigation could be categorized based on functional areas, departments, or products. The following are examples of types of investigations based on functional areas:

1. Manufacturing investigations
   These must identify not just what lot was affected by the issue, but any other lots that may have been affected (same product or different).
   For example, a freeze dryer was found out of calibration after producing product X lot Y. All products must be investigated going back to last calibration. This is critical as some will likely be in the field and may call for a field alert.
2. Complaint investigations
   This is an additional complication that product has not been in the field.
   Loss of control means others may have caused the complaint situation.
   Take, for example, broken tablets. Was this a problem with the manufacturing batch or was this bottle mishandled?

During the investigation, you must look for causes; do not take the Band-Aid™ approach. Identify appropriate corrective action that will prevent the issue from recurring. Verify and validate effectiveness. Do not merely confirm that something happened. For example, if an SOP was revised, find out why it was revised. If that SOP was revised because steps were lacking on the procedure and you had nonconforming issues as a result, you should then validate the effectiveness of that corrective action. Monitor over time, maybe over a month or over 3 months, whatever length of time is appropriate. Then when the offending issue has ceased occurring, document that you have monitored and validated the effectiveness of that corrective action. That way, you have thoroughly completed the process; you have closed the loop. You have effectively eliminated a problem, and you know it will not recur because you have tested and monitored its elimination. You have validated the effectiveness of your action plan.

Information may not be completely accurate or reliable

In some instances, an investigation may be triggered based on trends. The organization needs to be careful about data sources and the integrity of such data

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because, in some cases, the information may not be completely accurate or reliable. This is why a correct data collection and analysis program needs to be established up front.

Take, for example, a complaint of an unusual odor. Does the product smell different from other batches, or is it just the characteristic odor of the product that the person objected to? In either case, we still must investigate to ensure there is no product issue.

A set of specific instructions should be created to outline what must be done to determine the contributing and root cause of the problem. The investigation procedure should vary depending on the circumstances, but it must incorporate a comprehensive review and analysis of all of the circumstances related to the problem. Consider equipment, materials, personnel, procedures, design, training, software, and external factors.

Responsibilities/resources

- An important part of the investigation procedure is to assign responsibility for conducting each aspect of the investigation.
- Any additional resources that may be required are also identified and documented. For example, specific testing equipment or external analysis may be required.

Analysis

- The investigation procedure that was created is now used to investigate the cause of the problem.
- The goal of this analysis is primarily to determine the root cause of the problem described, but any contributing causes are also identified.
- This process involves collecting relevant data, investigating all possible causes, and using the information available to determine the cause of the problem. It is very important to distinguish between the observed symptoms of a problem and the fundamental (root) cause of the problem.

Data analysis

- Analysis is to gather data.
    - Complete information.
    - Understand the event.
    - The actual facts and root causes associated with the event/failure have been identified.
    - Corrective and preventive actions can be implemented.

In this step of the process, a procedure is written for conducting an investigation into the problem. A written plan helps to assure that the investigation is complete and nothing is missed. The procedure should include an objective for the actions that will be taken, the procedure to be followed, the personnel that will be responsible, and any other anticipated resources needed.

Investigation procedure

A set of specific instructions are created that outline what must be done to determine the contributing and root cause of the problem. The investigation procedure will vary depending on the circumstances, but it must incorporate a comprehensive review and analysis of all of the circumstances related to the problem. Always consider equipment, materials, personnel, procedures, design, training, software, and external factors.

Responsibilities/resources

- An important part of the investigation procedure is to assign responsibility for conducting each aspect of the investigation.
- Any additional resources that may be required are also identified and documented. For example, specific testing equipment or external analysis may be required.

The key to establishing a successful program is to make sure that it is fully understood by those who use it.

It is critical that companies determine if appropriate sources of product and quality problems have been identified. These data sources should include the following:

Internal data sources

- Acceptance activities
- Inspection and test data
- Component, in-process, and final test results
- Nonconforming product
- Scrapping or reworking
- Process monitoring
- Process control data, control charts, or SPC
- Equipment monitoring
- Calibration and maintenance
- Device history records
- Change control records
- Internal data sources
- Quality audit reports
- Internal audits
- Third-party audits (ISO, FDA)
- Scrap and yield data trends
- Supplier quality and performance data
- Equipment calibration
- Emergency equipment maintenance
- Training issues
- Device history records
- Batch history records
- OOS results
- Deviations

External data sources

- Complaints
- Medical device reports
- Adverse event reports
- Vigilance reports
- Service records
- Warranty and non-warranty
- Field service reports
- Returns
- Recalls
- Legal claims
- Articles and literature reviews

This chapter describes the process used for the investigation of quality events associated with products, processes, and quality systems to sufficiently determine investigation conclusions and provide possible courses of actions.

Introduction of the investigation process

A set of specific instructions for determining the contributing causes of the problem is written. This procedure directs a comprehensive review of all circumstances related to the problem and must consider the following:

- External factors
- Software
- Training
- Design
- Procedures
- Personnel
- Materials
- Equipment

The investigation consists of a planned and documented analysis of the events and the circumstances contributing to the problem. An investigation plan is written to assure that the investigation is complete and thorough, and it includes the following:

- Type of investigation in accordance with the risk evaluation results, trend results, CAPA review, or management review instructions
- Data to be collected
- Methodologies and procedures to be followed
- Personnel that will participate in the investigation
- Any additional resources (financial, equipment, etc.) that should be identified and documented
- Plan time lines with assigned responsibilities

The investigation could involve any combination of experiments, testing, data collection and review, statistical analysis, group problem-solving techniques, interviews, and product inspections. It is important to assign ownership and responsibility for each aspect of the requested investigation.

The investigation results and conclusions will include the following:

- A detailed description of the causes of the event or nonconformity
- A risk evaluation update (if required)
- A recommendation(s) of the corrective and/or preventive action(s) that may be taken (if required as a result of the investigation)

Investigation initiation

Most companies have assigned a CAPA coordinator, who typically ensures the initiation of the documentation for the investigation is appropriately completed. This includes assigning a sequential investigation number. The investigation number is the identification serial to be inserted in the investigation database or log.

The investigation database (or log) is typically controlled as a Quality List managed by the CAPA coordinator. The investigation database is an electronic file, which should be secure and backed up daily. The investigation database could consist (at least) of the following fields:

- Unique identifying number for the investigation process
- Risk evaluation number and revision
- Reference number and revision (NCR, complaint, or other)
- Date of initiation
- Initiator
- Site/department
- Product involved (machine or accessory)
- Process involved
- Description of the quality event associated with the investigation process
- Source of the quality event (e.g., NCR, CAPA review/management review, other)
- Risk priority number
- Risk priority level
- Investigation owner
- Deadline for investigation plan submission to CRB
- Effective closure date of the investigation plan
- Date of approval of the investigation plan (by CRB)
- Investigation status
- Expected closure date of the activities described in the investigation plan
- Effective closure date of the activities described in the investigation plan
- Risk evaluation number after the completion of the investigation plan
- Investigation conclusion (approved/rejected)
- Categories of the problem cause
- CAPA number and revision (if applicable)
- Notes and update by the CAPA coordinator
- Corrective action required (if applicable)
- Preventive action required (if applicable)

Investigation owner and team designation

Individuals to be responsible for the investigation preparation and realization are designated by the CRB or delegates. This assignment, including the investigation deadline, is documented in the investigation form.

Team constitution

An important part of the investigation procedure is to assign responsibility and resources for conducting each aspect of the investigation. The investigation owner is responsible for identifying the skills and competence levels required to carry out the investigation and for requesting the appropriate internal or external resources and expertise. Any additional resources that may be required are also identified, documented, and submitted to the CAPA Review Board for approval, for example, specific testing equipment or external analysis that may be required.

Investigation methodologies definition/selection

There are many methods for performing problem cause analysis. The investigation owner can select and set forth the most appropriate analysis methods for the type of investigation being performed.

Investigation plan elaboration

The investigation owner is typically responsible for the creation of a detailed investigation plan for submission to the CAPA Review Board. The plan is based on the risk evaluation results, or on the CAPA Review or Management Review Board's request, and it should include the overall objective and the different steps and activities for conducting the investigation. Timelines, with associated completion dates and responsibilities for each step, are also defined in the plan.

In addition, the investigation owner should provide information about the following:

- How are the data going to be obtained to make the foundation of the investigation or what the data mean apparent?
- What are the tools or measuring systems to be used in the investigation? Their unique identification also has to be provided. This information is used to trace each tool's calibration to ensure that data are valid and can support the objective evidence.
- The description of documentation, components, parts, labeling, packaging, and processes that should be examined to help reviewers to understand the collected data and conclusions should be included.
- The description of the investigation methods is needed.
- The description of pass/fail criteria, when appropriate (e.g., criteria established when conducting tests or engineering analysis to determine what constitutes a successful outcome), should be supplied.

The investigation owner and the approved team members should be allocated to the scheduled activities, and the consequent workload for each of them should be defined. The expected completion date should also be defined in the plan.

Investigation plan approval

The investigation plan should to be submitted to the CAPA Review Board for approval, and if the investigation plan is rejected, then the investigation team should resubmit a revised investigation plan by amending the original investigation plan. Previously approved investigation plans may be used, if available. The CAPA Review Board can delegate a few selected people for the approval of the investigation plan. The CRB's (or delegates') approval of the investigation plan and the estimated completion date is documented in the investigation form.

Execution of the investigation

The goal of the analysis is to determine the cause of the problem and identify any additional contributing causes. This process involves collecting relevant data, identifying possible causes, and using the information available to determine the cause of the problem. It is very important to distinguish between the observed symptoms of a problem and the cause of the problem.

Potential causes and data collection and analysis

At the beginning of the investigation, a list of possible causes is created. This will form the basis for collecting relevant information and test data, and it will provide the investigation owner with information to decide the most appropriate investigation methods to be utilized. For example, consider the situation where a large batch of parts from a monitor final testing phase was discovered to be nonconforming. There are many possible causes for this condition, including operator error, incorrect software, an uncalibrated tool, a material problem, a design problem, etc. By considering possible causes, appropriate information and data can be collected that will ultimately be used to determine the origin of the problem.

Results and data

The results of the data collection activities are documented and organized. This may include a combination of test results and/or a review of records, processes, service information, design controls, operations, and any other data that may lead to a determination of the cause of the problem. The resulting documentation should be complete and address the possible causes that were previously determined.

Problem analysis

The problem analysis is the conclusive interpretation of the data gathered in the previous steps. The analysis tools may vary from general problem-solving techniques to very specific elaboration programs for the determination of the reason behind a problem occurrence.

Investigation results submission

The assigned investigation team should summarize the conclusions. The team should take into consideration how did one or more of the following categories contribute to the quality event being investigated:

- Training/qualification, organization/planning, supervision
- Change management design
- Purchasing/supplier, quality manufacturing/installation operations
- Maintenance testing documentation
- Other (list other categories as required)

The cause(s) of the problem is thus documented. This is essential for determining the appropriate (if any) corrective and/or preventive actions that must be taken.

The investigation owner should determine if the event being investigated is broader in scope or of higher risk than was originally identified.

If an expansion of the investigation is required, the investigation continues until the cause(s) of the problem(s) is determined or justification for closing the investigation is approved by the CAPA Review Board.

The risk evaluation update

If during the course of the investigation new information indicates the initial risk evaluation was incorrectly estimated, the investigation owner should initiate an update of the original risk evaluation. If the updated risk evaluation indicates the risk has been reduced to an acceptable level, the investigation may be closed if approved by designated personnel.

In all cases before closing the investigation, the initial risk evaluation should be revisited for relevancy. This activity is documented also in the investigation form.

Investigation results approval

The CAPA Review Board should review the investigation file for soundness of data, investigation summary of results, and conclusions. If the investigation results and/or conclusions are not accepted, the investigation team should amend the investigation plan to perform additional investigational activities.

In most cases, companies have CAPA boards that will make the ultimate decision as to which event should be elevated to a CAPA, and typically the CAPA Review Board is responsible for the following:

- Prioritizing investigations
- Allocating resources for implementing investigations, as required
- Reviewing and approving investigation results

The investigation owner is responsible for the following:

- Developing investigation plans
- Ensuring that the investigation plan is executed
- Presenting the investigation results to the CAPA Review Board
- Updating the Nonconformance Risk Evaluation as required
- Completing the final Nonconformance Risk Evaluation report and determining if the investigation is to be closed or a CAPA is required

The CAPA coordinator is responsible for the following:

- Completing the initiation section on the investigation form
- Assigning investigation numbers
- Coordinating investigation activities with the CAPA Review Board as required
- Archiving the completed investigation form and the investigation report

Ensure accurate documentation

- Assign responsibilities to ensure root cause analysis (RCA) and CAPA issues are handled in a timely manner.
- Maintain accurate RCA and CAPA documentation using proper procedures.
- Outline the databases, logs, and computer systems used in a CAPA program.
- Revisit how to keep adequate routine reports and establish a good audit trail.

Step 5: investigation part II: out of specification

Out of specification investigations

The FDA considers the integrity of laboratory testing and documentation records to be of fundamental importance.

Laboratory testing is necessary (211.165) to confirm that components, containers and closures, in-process materials, and finished products conform to specifications, *including stability.*

Identifying and assessing OOS requires the following:

- An investigation should be conducted whenever an OOS results is obtained.
- Determine the cause of OOS.

- Batch rejection does not negate the need to perform an investigation.
- Is the result associated with other batches?
- A written record of the investigation should be made, including the conclusions of the investigation and follow-up.

The investigation should be *thorough, timely, unbiased, well-documented, and scientifically defensible*.

The first phase of investigation should include an initial assessment of the accuracy of the laboratory data before test solutions are discarded.

Investigating and assessing OOS results—principles of failure investigation

The failure investigation should consist of a timely, thorough, and well-documented review.

- The reason for the investigation should be clearly identified.
- *The manufacturing process sequences that may have caused the problem should be summarized.*
- Results of the documentation review should be provided with the assignment of actual or probable cause.
- A review should be made to *determine* if *the problem has occurred previously.*
- Corrective actions taken should be described.
- Laboratory phase of failure investigation—retesting
- The decision to retest should be based on sound scientific judgment.
- Retesting should be performed by an analyst other than one who performed the original test.
- Methods and specifications for the original test must be followed.
- The number of retests to be performed on a sample should be *specified in advance* based on scientifically sound, supportable principles.
- The number of retests should not be adjusted depending on the results obtained.
- Testing into compliance is objectionable under GMPs.
- The testing procedure should contain a point at which the testing ends and the product is evaluated.
- If, at this point, the results are unsatisfactory, the batch is suspect and must be rejected or held pending further investigation.
- Laboratory phase of failure investigation
    - Averaging

In some cases, a series of test results may be part of the procedure. If some results are OOS and some are within specification, the passing results should be given no more credence than the failing results. Relying on the test data averaging in such a case can be misleading.

- For example, in an assay within a given range of 90–110%, test results of 89%, 89%, and 92% would produce an average of 90%, even though two of the assay values represent failing results. *To use averaged test results for assay reporting, all results should conform to test specifications.*
- Reporting of OOS-related failures—reporting to FDA

For those products that are subjects of applications, FDA regulations require submitting within 3 working days a field alert report of information concerning any failure of a distributed batch to meet any of the specifications established in an application (21 CFR 314.8(b)(1)(ii)).

The following exhibits provide guidance for laboratory investigations (Exhibit 8.1–8.6):

Exhibit 8.1 Phase I laboratory investigation

4 Manager and Chemist — **Perform Phase I of the laboratory investigation, using Phase I Laboratory Investigation Form as a guide.**

Investigation should include, but not limited to, a review of the following:

- **Correct test method used and followed.**
- **Correct sample used.**
- **Power stability**
- **Equipment calibration**
- **Equipment functions**
- **Standards prepared correctly and used.**
- **Standard history**
- **Reagents prepared correctly and used**
- **Sample and standard dilutions performed correctly**
- **Entries into calibration files**
- **System suitability**
- **Integration**
- **Calculations**

a. **If the Phase I laboratory investigation identifies an assignable laboratory error, continue to step 5.**

b. **If the Phase I laboratory investigation does not identify an assignable laboratory error, go directly to step 13. (Phase II)**

Exhibit 8.2 Phase I laboratory investigation

5 Chemist — **Record the following in the laboratory notebook near the original OOS value.**

a. **Laboratory error that was identified**

b. **OOS Number (from OOS Log)**

c. **Reference to record of follow-up repeat testing.**

6 Chemist — **Sign and date notebook adjacent to the entries.**

7 Manager — **Assign original chemist and an additional chemist to repeat the test.**

8 Chemists (each) — **Repeat the test. Begin testing procedure again, using the original laboratory sample and test method. Report results to Manager.**

9 Manager — **Review results.**

If results reported by each analyst agree within two standard deviations of the intermediate precision for the method, continue with Step 10.

If the results reported by each analyst do not agree within two standard deviations for the intermediate precision for the method, go directly to Phase II, Step 13.

10 Manager — **Assure that the Phase I Investigation Form is complete.**

Identify the cause of the original result.

If appropriate invalidate the original result. Assure that original result is retained.

11 Manager — **Report the average of the results from the two analysts.**

12 Manager — **Initiate a Minor deviation. (QA ***). Cross reference laboratory records in the Deviation Report. (MF ***7)**

Note — **This concludes the Laboratory Investigation.**

Exhibit 8.3 Phase II laboratory investigation

Phase II Laboratory Investigation

13	Manager	Determine if the laboratory sample is suitable for retesting. If it is suitable, go directly to Step 18. If laboratory sample is not suitable because of limitations defined procedurally (i.e., stability) sample in accordance with the original sampling procedure, go directly to Step 15. If it is not suitable, and it has not been anticipated procedurally, continue with Step 14 below.
14	Manager	Initiate a Major deviation (QA ***), citing unsuitable sample as the observation.
15	Chemist	Prepare a resampling plan. Include: • Justification for not using the original sample and resampling. • Material identification to be sampled • Justification for new sample • Sampler (by position) • Sample size (if this is different from original sampling plan, justify) • Sample location (if this is different from original sample locaton, justify) • Sample container • Sample size Sign and date resampling plan. Submit to Quality Assurance for review and approval.
16	Quality Assurance	Review and approve resampling plan.
17	Designated sampler	Execute resample plan. Submit sample to the laboratory
18	Manager	Determine if there is a retest protocol for the current situation. If the test is an HPLC assay for an active, continue with Step 19 below. For all other situations, go directly to Step 24.
Note		Steps 19 to 23 are a retest protocol for on OOS resulting from a HPLC test for an major component in a formulation on the active in the bulk Active Pharmaceutical Ingredient.
19	Manager	Assign retest to two chemists. Note: The original Chemist may be one of the two assigned Chemists. Assign one of the chemists to collect and analyze the data (Analyzer).

Exhibit 8.4 Phase II laboratory investigation

20	Chemists (each)	Perform retest. Perform the test procedure defined in the test method in duplicate. Note: If the procedure requires that the chemist prepare one standard and three samples, the retest chemist will prepare two sets of one standard and three samples and handle each set independently and make the defined number of replicate injections. Calculate the areas from the replicate injections in accordance with the procedure. Procedure acceptance criteria for the replicate injections must be met. If they are not, the injections are repeated. Calculate the average result for each of the sample preparations for each test procedure. Results must be within two standard deviations of the method repeatability, identified in the method validation. If they are not, a new set of samples must be prepared and tested. Average the replicate tests for each test procedure. Evaluate the duplicates of the test procedure. The duplicates of the test procedure must be within two standard deviations of the method repeatability. If they are not the retest protocol must be started over. If any of these acceptance criteria are not met, the corrective action must be performed and a DCT deviation initiated. Provide Analyzer with the reportable results for each of the sample preparations. Report the individual results, average, standard deviation, and relative standard deviation.
21	Analyzer	Evaluate the combined results. The averages for the analyst must agree within two standard deviations of the intermediate precision for the test method reported in the method validation.

Exhibit 8.5 Phase II laboratory investigation

22	Analyzer	Determine the average, standard deviation, and relative standard deviation of the combined values. If the original value (OOS or unexpected) is greater than three standard deviations from the average of the retest, it is considered an outlier and not representative of the material. The reportable value is the average of the retests. If the original value is within two standard deviations of the average of the retests, the original is representative of the material. If the original value is out-of-specification and average of the retests is within specification, both the original value and the average of the retests are reported. They cannot be averaged. If the original value is unexpected, but within specifications, and the retest is within specification, the reportable value is the average of the original and retests. If the original and retests are out-of-specification, the reportable value is the average of the original and the retests. If the original value is between two and three standard deviations, the retest may be extended for one additional retest protocol.
23	Analyzer	Continue to Step 28.
24	Manager	Prepare a protocol for the retest. Protocol should include: Reason for retest. Sample to be tested. Test Method to be used. Chemists assigned to conduct the retest. There should be at least two Chemists involved in the retest protocol. One may be the original Chemist. Number of sample preparations by each Chemist. Number of replicate injections or readings of each preparation. Who will evaluate the results (Analyzer). Acceptance criteria. Sign and date the protocol. Submit protocol to Quality Assurance.
25	Quality Assurance	Review and approve protocol.
26	Manager	Assign retest to chemists.
27	Assigned Chemists (each)	Execute protocol. Provide results to Analyzer.

Exhibit 8.6 Reporting results

Reporting the results

28	Analyzer	Complete data evaluation in accordance with protocol. Submit results to Manager.
29	Manager	Review and approve report.
30	Manager	Enter reported results onto Certificate of Analysis.
31	Manager	If the retest results confirm the original OOS, initiate a Major deviation.
32	Manager	Close out OOS logbook entry.

- Case studies—FDA citations investigations
  - The batches placed on stability testing each year are not a representative sample of the batches manufactured during that year.
  - Failure of a stability sample should trigger a review or testing of other batches manufactured during the year.
  - The investigation report does not include the corrective actions necessary to prevent similar recurrences. *Reports do not indicate if similar OOS results were reviewed or if other lots were affected.*
  - There is no SOP for conducting product investigations or tracking product failures.
- Retesting
  - Failure to investigate, justify, and record deviations from written specifications and test procedures when repeated testing is done, due to initial test failures
  - Averaging passing and failing results without investigating cause of OOS
  - Discarding test data without just cause

Step 5: investigation part III—complaint investigation

Investigation of complaints

In this section, we will be reviewing a process that can be used for the investigation of the complaints, for performing the risk analysis for complaint investigation, and for taking the determination after the investigation, as a detailed description of the investigation process.

The objective is to ensure that all received complaints are evaluated and investigated, based on the risk level, to determine the cause of the problem and the most appropriate corrective and/or preventive action(s).

The Complaint Handling Unit (CHU) is typically in charge of the process of investigation of complaints of a company as a part of the process of complaint handling. The complaints to be submitted to the investigation are typically filed in a complaint database of XYZ products.

At a minimum, the process of investigation should be composed of the following steps:

- Assignment of the investigation owner
- Preliminary estimation of the risk associated with the complaint and determination of the extent of the investigation
- Investigation planning (if required)
- Investigation execution
- Investigation reporting
- Approval of the investigation report.

Complaints investigation process

The CHU group should review and evaluate all complaints to determine if an investigation is required.

An effective complaint investigation will provide information about the cause(s) of the problem to support the development of an appropriate corrective and preventive action as applicable.

A complaint investigation is required when the following are true:

- When the complaint was classified as potentially reportable in the vigilance classification process (Class I complaint)
- In case of alleged malfunction of the device
- In case of failure of labeling or packaging
- In case of actual or alleged harm

In case of malfunctions of the device with no harm, if the complaint is for the same product and of the same problem of a previously investigated complaint, a new complaint investigation may not be required.

An investigation is not required in the following cases:

- For complaints reporting events where a similar event was yet filed as a complaint and investigated
- For complaints about matters that do not have direct impact on the therapy effectiveness or on the use of the device (e.g., request of new features or of new commercial configurations or availability of a new spare part)

The decision for investigating is taken by the investigation owner. The rationale for no investigation should be recorded by the investigation owner in the database module for the initiation of the investigation.

Investigation owner assignment

The investigation owner is assigned to investigate a complaint or a group of complaints by the CHU manager.

Risk basis—preliminary risk assessment of complaints

The extent of the investigation should be evaluated following the estimation of the risk represented by the event reported in the complaint. However, the extent of the investigation should be adequate for addressing the appropriate corrective actions for the risk represented by the complaint or for the dissatisfaction of the customer.

The company should have a complete list of hazards and harms listed for each therapy and that should be the basis for determining the risk and the level of investigation required. The severity rating for each harm of the listing should determine the level of investigation.

The severity level associated with the complaint should be determined following a risk management procedure. The extent of the investigation should be determined following the criteria below:

- If the severity rating of the complaint is lower than or equal to 3 and the likelihood of occurrence of the failure is occasional, remote, or improbable, minimum extent investigation and trending are required.
- If the severity rating of the complaint is lower than or equal to 3 and the likelihood of occurrence of the failure is probable or frequent, full investigation is required.
- If the severity rating of the complaint is higher than 3, the full investigation is required.

In case of malfunctions and when the product Failure Mode and Effects Analysis (FMEA) is not available, the severity associated with the complaint may be determined with alternative methods, such as by means of a review of complaints reporting death and serious injury in the complaint files of the products. If there are complaints reporting harms as a consequence of a failure, the severity associated to the failure will be the severity of the harm.

For complaints where a patient injury is alleged, the full investigation is required.

Complaint investigation plan

The investigation owner establishes a complaint investigation plan for all complaints requiring full investigation. For system-level complaints, an investigation plan is mandatory. The complaint investigation report is used to document the actions and results obtained by executing the investigation plan. The plan is approved by the CHU manager.

Complaint investigation execution

The following steps should be considered for complaint investigation:

- Timeline and deadline with associated completion dates and responsibilities for each step
- Description of the investigation methods
- Tools or measuring systems to be used in the complaint investigation
- Documentation, device history record (DHR), components, parts, labeling, packaging, and processes to be investigated
- Other lot numbers or products that could be affected by the same failure mode
- Description of pass/fail criteria, when appropriate, e.g., criteria established when conducting tests or engineering analysis to determine what constitutes a successful outcome

The full investigation should include the following:

- Label and labeling review
- Root cause analysis
- Medical evaluation (in case of alleged harm)
- Final risk review

The minimum extent of investigation is requested for all types of complaints, and this will include the following:

- A check of the failure mode
- A check of the immediate cause
- The preliminary risk evaluation

Root cause analysis

CHU, when requested, should perform a quest of the cause(s) of the event reported in the complaint in a sufficient way to determine the action to be taken for an effective corrective and/or preventive action.

The tool that normally is used by CHU in the cause quest is the RCA. The work instruction of WI176 “Root Cause analysis” is adopted as reference for this analysis.

The team of the RCA is normally constituted of a CHU investigator and at least one product expert (belonging to the Product Development or Quality department).

The typical data to be collected

The cause–effect analysis is typically documented by means of a fishbone diagram (see RCA SOP).

The typical categories of potential causes to be adopted in the RCA of complaint will be material, machine, manpower, and environment.

The category *Material* should include, as an example, an analysis of disposables used (type, production lot), cleaning materials and products, disinfection material and products, and other devices used in conjunction with a certain device to deliver the therapy.

The category *Machine* should include, as an example, an analysis of serial number and configuration of that machine as determined by DHR, software revision, history of the maintenance and of the service interventions, recording of the history of the treatment (alarms, etc.), weaknesses of the design, weaknesses of the procedures of manufacturing, and weaknesses of the procedures of maintenance.

The category *Manpower* should include, as an example, an analysis of skill of the users and of the personnel, training of the users and of the personnel, possible inadequate operating procedures, and possible inadequate working conditions.

The category *Environment* should include, as an example, an analysis of supply of water, supply of concentrates (if not delivered through a disposable device), environment temperature, power supply stability, moisture and noise, networking configuration, and networking conditions.

The RCA may include a verification and documentation that the cause is able to produce the reported effect. The verification should be conducted above the reasonable level of doubt that the link between the effect and the cause is found.

Medical evaluation

A medical evaluation of the event reported on the complaint is necessary in case of actual or alleged harm of the patient.

This medical evaluation should verify the following:

- Did the device actually cause or contribute to the harm?
- Is the injury of the complaint a serious injury as per definition of the regulation?
- What is the severity classification of the injury?

The medical evaluation report should include adequate rationale for each determination taken. The medical evaluation should be done by a medical expert and approved by the company's chief medical officer.

Labeling review

The label and labeling evaluation is performed to verify proper labeling and to detect if user errors caused by labeling or design deficiencies have occurred.

The labeling evaluation should be documented in the complaint investigation report.

This review should include at least the following:

- The estimation of the severity based on the results of the medical evaluation
- The estimation of the probability of harm

The results of the final risk review of the complaint should be documented in the complaint investigation report.

Complaint investigation report

The complaint investigation owner is typically responsible for finalizing the complaint investigation report.

The report of complaint investigation should include the following:

1. Name of the device
2. Any device identification(s) and control number(s) used
3. The name, address, and phone number of the complainant
4. The nature and details of the complaint
5. The dates and results of the investigation
   As a minimum, the complaint investigation results should contain the following:
   a. Failure mode
   b. Immediate cause
   c. Root cause
   d. Actual or potential harm to the patient with the associated severity of harm rating
   e. Risk action priority level (RAPL: R1, R2, or R3)
6. Medical evaluation
7. Label and labeling review
8. Any corrective action taken
9. Any reply to the complainant

The following decisions should be considered as part of the complaint investigation report:

1. Should a CAPA evaluation be requested?
2. Should a risk management file evaluation be requested?
3. Should a design change evaluation be requested?
4. Is there any technical or medical reason connected with the characteristics or performance of the device that could lead to systematic field action of devices of the same type by the manufacturer? If yes, an evaluation by the corrections and removal process is required.

A copy of all complaint investigation results and all supporting documentation will be forwarded to the respective groups.

Report review and approval

The complaint investigation report should be reviewed and approved by the CS manager in case of complaints of Class I or by the CHU manager in case of complaints of Class II.

In case the investigation report is not approved, appropriate actions should be initiated, such as revising the document or restarting the investigation.

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Step 6: part I—root cause analysis

9

The sixth step is the performance of the root cause analysis (RCA). Once the data is analyzed, pull it all together to get to the root cause or causes of the problem. Like a detective solving a mystery, some aspects may appear obvious, while others may be more obscure. You may have to return to the data time and again for clarification while you consider and eliminate possibilities until you arrive at the root cause. In this chapter, we will be looking at the systemic approach to RCA as well as tools that can be used to perform the analysis.

RCA is recognized as a good quality management technique; it is normally used as a tool during a process of investigation. The RCA consists of a process of systematic evaluation to identify the most basic cause of an **effect**. Generally speaking, an effect could be any of the following:

• Positive variation in performance	➔ it is referred as an objective
• Negative variation in performance	➔ it is referred as a problem

The primary purpose of the RCA is as follows:

- To identify root cause(s) so that these latent failures may be eliminated or modified and future occurrences of similar problems or mishaps may be prevented
- To establish common terminology in the company's community to facilitate improved communication and understanding
- To allow learning from the past problems, failures, and accidents

Every RCA should be documented in a specific Root cause analysis **(RCA)** Root cause analysis report **(RCAR)**. More than one RCA could be documented in a single RCAR for sake of completeness. A specific Root cause analysis report (RCAR) template must be available for each RCA.

Outcome

The outcome of the RCA is an RCAR that includes all the relevant information concerning the conducted analysis activity. A report should be written by the analyst(s) and signed by all the people involved, with the date of the analysis results identification.

CAPA in the Pharmaceutical and Biotech Industries. http://dx.doi.org/10.1016/B978-1-907568-58-9.00009-6

How to conduct an RCA and the RCA team

A dedicated working group has to be identified each time an RCA activity begins; this group is called **root cause analysis team (RCAT)**. The RCAT consists of a minimum of two individuals: one or more **analysts** and one or more **reviewers**.

- It is preferable to have as an analyst at least one person that does the work.
- It is preferable to have as reviewer one person with decision-making authority.
- It is also advisable to have as a minimum two reviewers: one senior (high skill) and one junior (less skill), so that the junior can learn and increase his/her skill.

The analyst(s) and the reviewer(s) have to be elected depending on the following:

- The complexity of the issue/anomaly under analysis
- The nature of the issue/anomaly under analysis (e.g., SW, HW, safety)
- Their knowledge of the specific argument under analysis

The RCAR must include the following:

- The name(s) of the analyst(s)
- The name(s) of the reviewer(s)
- The criteria used to define the analyst(s) and the reviewer(s)
- Who is assigned to the analyst(s) and the reviewer(s)

Definition of the problem

A clear identification of the problem should be conducted as a preliminary phase of each RCA. All the members of the RCAT have to participate in this phase to have a clear understanding of the problem and their charge. The RCAR must clearly indicate which of the following items are relevant for the problem's description and their contents:

- Incident/issue detailed description (including: what, where, when, who, how, and how many)
- Frequency of the occurrence (how many, how often, etc.)
- Similarity with previous known issues

Gathering relevant data

All the possible and relevant data should be collected and/or referred (in case of a remote information not easily collectable). This is useful to provide the RCAT with a suitable and extensive bench of information to work with during the following analysis of the problem.

The RCAR must clearly describe these items in terms of the following:

- Description of the item(s)
- Physical location of the described item
- Name(s) of the file(s) indicated as relevant data

Cause/effect analysis

In this phase, all the possible contributing causes have to be identified, sorted, and analyzed by the RCAT. A widely used tool is a fishbone or cause/effect analysis, which we will use as the first RCA tool.

Identification of the causes

This phase of the analysis could be conducted only by the RCAT or by the RCAT and other people (extended RCAT) in case some relevant information is already available and is in the hands of someone else.

As a possible method, the *brainstorming technique* is suggested to be conducted during this phase by the RCAT or the extended RCAT. During the activity aimed to identify the causes, the questions *what* and *why* should be continuously asked at each conjuncture of the process. The RCAR should indicate all the relevant causes that have been found by the RCAT.

Sorting and analysis of the causes

This is the real investigation phase of the process, and it should be conducted by the RCAT; normally in this phase, there is not the real need to involve other people outside the RCAT.

The method used in this case is the fishbone diagram (also called a cause and effect diagram).

This method consists of the construction of a structured and pictorial display of a list of causes organized to show their relationship to a specific effect. The steps for constructing and analyzing a cause and effect diagram are outlined below.

The RCAR should include the cause and effect diagram described below in a suitable and easy-to-edit graphic representation.

Cause and effect diagram: step 1

Step 1 concerns the identification and the definition of the **effect** to be analyzed. Its representation is shown in Exhibit 9.1.

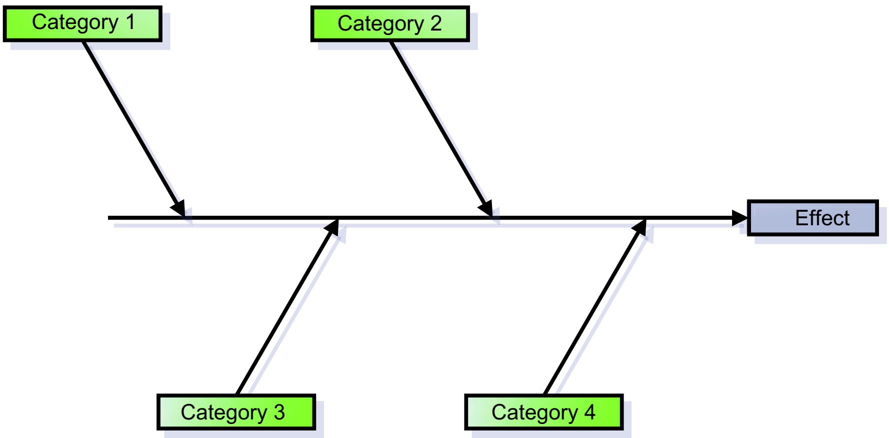
Exhibit 9.1

Cause and effect diagram: step 2

Step 2 concerns the identification and the definition of the **main causes** contributing to the effect being studied. These are the labels for the major branches of the diagram and become the **categories** under which to list the many causes related to those categories. These categories plus the effect represent the spines of the fishbone.

Its representation is shown in Exhibit 9.2.

Exhibit 9.2

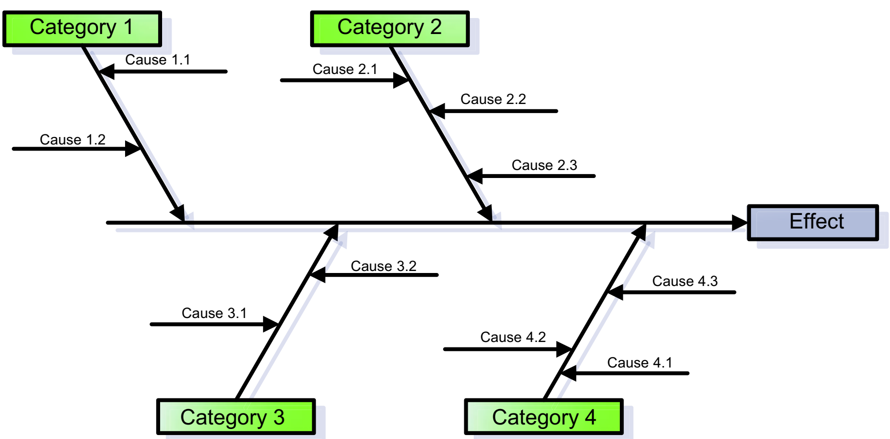


Cause and effect diagram: step 3

Step 3 concerns the identification and the definition of the **specific factors** that may be the causes of the effect. In this phase, as many causes as possible should be identified and attached as sub-branches of the major branches.

Its representation is shown in Exhibit 9.3.

Exhibit 9.3



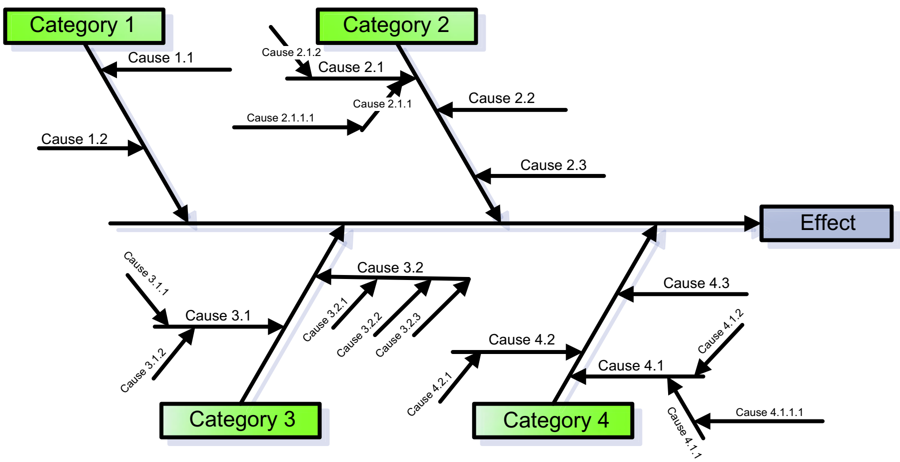
Cause and effect diagram: step 4

Step 4 concerns the identification and the definition of the **detailed factors** at the highest level of detail and their organization under the related causes or categories. This is the task that normally concerns the majority of the investigation time.

Note: During the activity aimed to identify the causes, the questions *what* and *why* should be continuously asked at each conjuncture of the process. The focus has to be given to the process itself, not to the people involved in the process.

Its representation is shown below in Exhibit 9.4.

Exhibit 9.4



At this stage of the details identification, it could be necessary to split the diagram into more than one sheet, for example, in the case of one branch with many sub-branches.

Cause and effect diagram: step 5

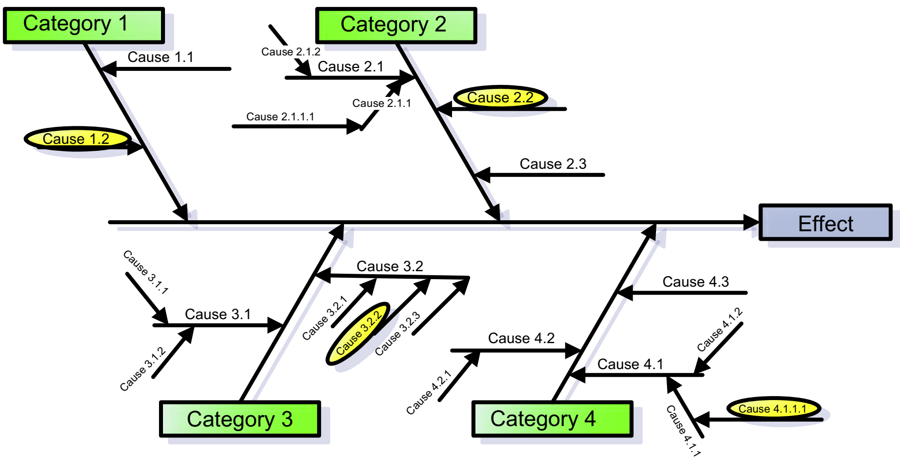
Step 5 concerns the **analysis of the diagram** to identify causes that warrant further investigation. Because *cause and effect diagrams identify only possible causes*, it might be necessary to further use a Pareto chart analysis to help the RCAT determine the causes to focus on first.

Analysis criteria:

- Particular emphasis should be given to the causes that appear repeatedly: these may represent root causes.
- Particular attention has to be given to every cause that could be measurable to quantify the effects of any changes.
- For the same reason, also focus on the unmeasurable causes and think about a possible way to make them measurable since it is possible to quantify only what is measurable.
- Once the RCAT has decided to take action on some particular causes, these must be well identified (e.g., by circling them).

Its representation is shown below in Exhibit 9.5.

Exhibit 9.5



Open issues/notes

The RCAR should also include all the remaining (if any):

- Open points
- Notes
- Doubts
- Remarks

Action plan

The detailed action plan will be produced by the person in charge of the specific project planning. This is not part of the RCAR, but it has to include the RCAR as a basic document for the action planning. This plan will include a compendium of the previously identified action items:

- The identification of the decided action to keep track of the action's execution (action IDs)
- The owner(s) of the action items (who)
- Method used to apply the action items (how)
- Time plan for action items development and V&V (when)

RCA assessment and maintenance

It is advisable to periodically assess the progress after the actions are taken. For this reason, it has to be decided what should be measured, by whom, and how often, and the RCAR should also include a section describing the guidelines for the periodic assessment of the actions taken to solve the issues that are the object of the RCA session itself.

Part II: RCA tools

Root cause investigations and tools

What is root cause?

Root cause is the fundamental breakdown or failure of a process that when resolved prevents a recurrence of the problem. In other words, for a particular product problem, root cause is the factor that when you fix it, the problem goes away and does not come back. RCA is a systematic approach to get to the true root causes of our process problems.

RCA is a method of problem solving used for identifying the root causes of faults or problems. A factor is considered a root cause if removal thereof from the problem fault-sequence prevents the final undesirable event from recurring; whereas a causal factor is one that affects an event's outcome but is not a root cause. Though removing a causal factor can benefit an outcome, it does not prevent its recurrence with certainty.

Root cause identification

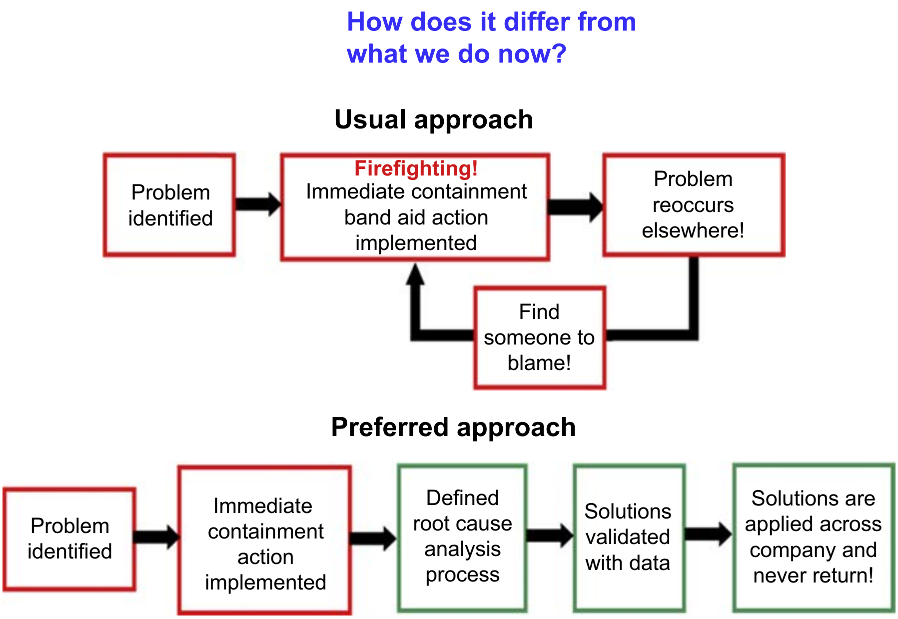
Current FDA expectations of a corrective action and preventive action (CAPA) program include a sound understanding of the product, ability to evaluate all the things that could possibly have caused the event (allowing us to get to the root cause of the problem), investigating the problem thoroughly, and comprehensive knowledge of the possible actions to be taken once we determine the root cause. From an FDA perspective and also from an ISO perspective, regulatory agencies demand that we go far beyond momentarily eliminating obstacles. We need to define and understand the root cause to correctly analyze the problem. Once we determine the root cause or causes, then we can begin to identify possible corrective actions. The regulatory expectation is that we identify not only what the problem is but what its cause is or what the many causes of that problem may be.

Because of this expectation, it also must be in our plan of action to indicate what we are going to do to implement the corrective action, and then within that plan of action, we need to identify what is the defined time frame in which we are going to act. The last part of the corrective action requirement is that we validate the effectiveness of the action that was taken. Therefore, we are required not only to take action, but through monitoring and verification of effectiveness to confirm that the corrective action was effective.

Determining the *whys*: It is critical to determine why an event or failure occurred and be able to specify *workable corrective measures that prevent future events*. Understanding why an event occurred is the key to developing effective recommendations.

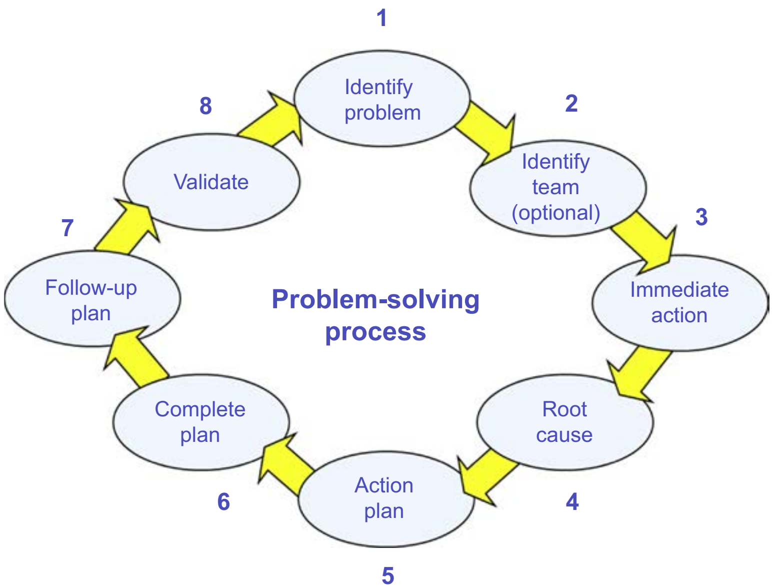
A thorough RCA must include an analysis of underlying cause and effect systems through a series of why questions, a determination of related processes and systems identification of risks and their potential contributions, a determination of potential improvement in processes or systems including participation by the leadership of the organization and those most closely involved in the processes, and that systems be internally consistent. Exhibit 9.6 shows an example of what most companies experience. Good or bad, most companies function in what most call firefighting mode.

Exhibit 9.6 Usual versus preferred approach



In today's environment, companies are in a constant fight for resources and time. As a result, companies often try to put out fires without understanding what caused the fire, and therefore, the event reoccurs over and over. A preferable method would be to have a systematic process approach such as the one shown in Exhibit 9.7.

Exhibit 9.7

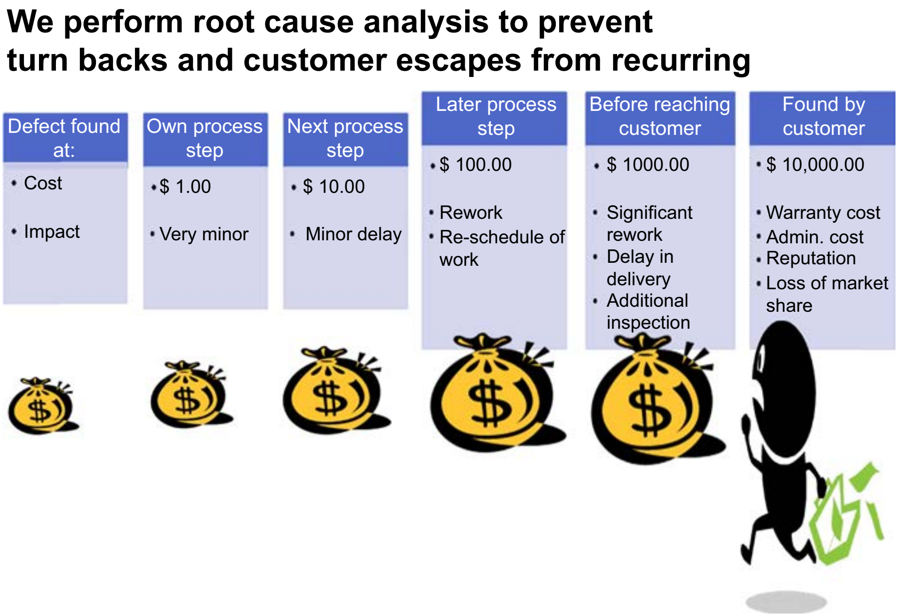


Philosophy of RCA

Each problem is an opportunity (golden nugget) because it can tell a story about why and how it occurred.

- It is critical that everyone take a personal and active role in improving quality.
- The true problem must be understood before action is taken.
  - Problems are often masked for a variety of reasons.
- To do this well, we must be
  - both focused and open-minded
  - both patient and quick
  - above all, relentless (Exhibit 9.8)

Exhibit 9.8



Symptom approach versus root cause

If we do a poor job of identifying the root causes of our problems, we will waste time and resources putting Band-Aids on the symptoms of the problem (Exhibit 9.9).

Exhibit 9.9 Symptom approach versus root cause

• Symptom approach	• Root cause
• Errors are often a result of worker carelessness.	• Errors are the result of defects in the system. People are only part of the process.
• We need to train and motivate workers to be more careful.	• We need to find out why this is happening, and implement mistake proofs so it will not happen again.
• We do not have the time or resources to really get to the bottom of this problem.	• This is critical. We need to fix it for good, or it will come back and burn us.

How do we do RCA?

Said simply, RCA is asking why the problem occurred and then continuing to ask why that happened until we reach the fundamental process element that failed. The following example illustrates the basics of RCA.

RCA major steps

The RCA is a six-step process involving the following:

- Situation assessment
- Organize and empower the ideal problem-solving team
- Data collection
- RCA process charting
- Root cause identification
- Recommendation generation and implementation
- Remember to get the facts
- Situation assessment
- Obtain evidence before, during, and after the incident
- Interview people
- Act quickly and begin the investigation
- Organize and empower the ideal problem-solving team
- Data analysis

Analysis is to gather data, and without complete information you will never gain a true understanding of the event, and the actual facts and root causes associated with the event/failure will not be identified. Always search for cause and effect relationships.

RCA process charting

Charting can provide a structure to organize and analyze the information gathered during the investigation and identify gaps and deficiencies in knowledge as the investigation progresses.

The chart can be a sequence diagram that describes the events leading up to an occurrence, plus the conditions surrounding these events. Preparation of the RCA chart should begin as soon as the RCA team starts to collect information about the occurrence.

Typical checklist for aspects to be considered when doing the RCA

Materials

- Defective raw material (does material meet specification?)
- Batch-related problem
- Design problem (wrong material for product, wrong specifications)

- Supplier problem (lack of control at supplier, alternative supplier)
- Lack of raw material

Machine/equipment

- Incorrect tool selection—suitability
- Inadequate maintenance or design—calibration?
- Equipment used as intended by the manufacturer?
- Defective equipment or tool
- End of life?
- Human error—inadequate training?

Environment

- Orderly workplace
- Properly controlled—temperature, pressure, particulate, cleanliness
- Job design/layout of work

Management

- Inadequate management involvement
- Stress demands
- Human factors
- Hazards not properly guarded
- Were management informed; did they take action?

Methods

- Procedures not adequately defined
- Practice does not follow written method
- Poor communications

Management system

- Training or education lacking
- Poor employee involvement
- Poor recognition of hazard
- Previous hazards not eliminated

Measurement, monitoring, and improvement

Inadequate measuring and improvement

Barrier analysis

Barrier analysis is an investigation or design method that involves the tracing of pathways by which a target is adversely affected by a hazard, including the identification of any failed or missing countermeasures that could or should have prevented the undesired effect(s).

This technique focuses on what controls are in place in the process to either prevent or detect a problem and might have failed (http://asq.org/learn-about-quality/root-cause-analysis/overview/root-cause-approaches.html).

Barrier analysis: pros and cons

Pros

- Conceptually simple, easy to grasp
- Easy to use and apply, requires minimal resources
- Works well in combination with other methods
- Results translate naturally into corrective action recommendations

Cons

- Sometimes promotes linear thinking
- Sometimes subjective in nature
- Can confuse causes and countermeasures
- Reproducibility can be low for cases that are not obvious or simple

Definitions

Barrier: A construct between a hazard and a target, intended to prevent undesired effects to the target. A barrier is often passive, i.e., its protective nature is inherent to its structure, and no additional action on the part of any agent is required to afford this protection.

Control: A mechanism intended to prevent undesired effects to the target. A control is often active, i.e., its protective nature is brought into being through the actions of an agent.

Countermeasure: A barrier or control intended to cut off a pathway between hazard and target.

Hazard: An agent that can adversely affect a target.

Pathway: A route or mechanism that provides the means or medium through which a hazard can affect a target.

Target: An object that requires protection or needs to be maintained in a particular range or set of conditions.

At the heart of barrier analysis is the concept of the target. The primary quality of a target is that it exists under a specified range or set of conditions and that we require it to be maintained within that specified range or set of conditions.

This very general quality means that almost anything can be a target—a person, a piece of equipment, a collection of data, etc.

Given the concept of the target, we then move to the means by which a target is adversely affected. By adverse effect, we mean that the target is somehow moved outside of its required range or set of conditions. Anything that does this is called a hazard.

This is a very general quality—almost anything can be a hazard. However, it is possible to uniquely define hazard/target pairs by the pathways through which hazards affect targets.

Having identified hazards, targets, and the pathways through which hazards affect targets, we arrive at the concepts of barriers and controls. These are used to protect and/or maintain a target within its specified range or set of conditions despite the presence of hazards. The primary quality of a barrier or control is that it cuts off a pathway by which a hazard can affect a target.

Barriers and controls are often designed into systems or planned into activities to protect people, equipment, information, etc.

All hazards may not be identified beforehand, or unrecognized pathways to targets may surface.

In both of these cases, appropriate barriers and controls may not be present. Even if they are present, they may not be as effective as originally intended. As a result, targets may lack adequate protection from change or damage.

The purpose of barrier analysis is thus to identify pathways that were left unprotected or barriers and controls that were present but not effective.

All pathways relate to specific hazard/target pairs, and all barriers and controls relate to specific pathways.

Success in barrier analysis depends on the complete and thorough identification of all pathways.

Change analysis

Change analysis is an investigation technique that involves the precise specification of a single deviation so that changes and/or differences leading to the deviation may be found by comparison to similar situations in which no deviation occurred.

This approach is applicable to situations where a system's performance has shifted significantly. It explores changes made in people, equipment, information, and more that may have contributed to the change in performance (http://asq.org/learn-about-quality/root-cause-analysis/overview/root-cause-approaches.html).

Definitions

Change: A discrete difference between an occurrence exhibiting the deviation and a similar occurrence that did not exhibit the deviation
Deviation: A situation in which actual results or actual performance differed from what was expected

Pros and cons

Pros

- Conceptually simple, easy to grasp
- Works well in combination with other methods
- Results translate naturally into corrective action recommendations
- Can be used to find causes that are obscure or that defy discovery using other methods

Cons

- Requires some basis for comparison
- Resource intensive, requires exhaustive characterization of deviation
- Applicable only to a single, specific deviation
- Provides only direct causes for a deviation
- Results may not be conclusive, testing usually required

Discussion

As suggested by the name of the technique, change analysis is based on the concept that change (or difference) can lead to deviations in performance. This presupposes that a suitable basis for comparison exists.

What is then required is to fully specify both the deviated and undeviated conditions and then compare the two so that changes or differences can be identified. Any change identified in this process thus becomes a candidate cause of the overall deviation.

What is a suitable basis for comparison?

There are basically three types of situations that can be used.

First, if the deviation occurred during performance of some task or operation that has been performed before, then this past experience can be the basis.

Second, if there is some other task or operation that is similar to the deviated situation, then that can be used.

Finally, a detailed model or simulation of the task (including controlled event reconstruction) can be used, if feasible.

Given the full specification of the deviated condition, it becomes possible to perform a detailed comparison with the selected undeviated condition. Each difference between the deviated and undeviated situations is marked for further investigation. In essence, each individual difference (or some combination of differences) is a potential cause of the overall deviation.

The purpose of change analysis

The purpose of change analysis is thus to discover likely causes of a deviation through comparison with an undeviated condition and then to verify true causes by testing.

Change analysis may at times be the only method that can find important, direct causes that are obscure or hidden. Success in change analysis depends ultimately on the precision used to specify a deviation and in verification of true cause through testing.

It is important to probe the process and some of the following questions:

- Was the procedure followed?
- Is the documented procedure wrong?
- Did the employee do anything else?
- Did the employee know this was wrong?
- Was there a lack of practice?
- What was the employee doing during this time?
- Did the employee use the correct techniques?
- Did the employee use the wrong method?
- Did the employee use the wrong tools?
- What was the probing process?
- What was the flow chart correct process?
- Was there an interview of personnel and flow chart process as described by personnel (RCA chart)?
- What is the current process?
- Are they the same?
- Compare!

An RCA chart can be used to identify the underlying reason or reasons for each process step or possible error. A process map structures the reasoning process, and it will help the team to answer questions about why particular causes that have occurred.

Additional effective RCA tools include the following:

- Brainstorming
- Cause and effect analysis
- Why diagrams
- Control charts
- Scatter plots
- Check sheets
- Pareto charts
- FTA (fault tree analysis)

Brainstorming

What is it?

Brainstorming is a process in which a group quickly generates as many ideas as it can on a particular problem and/or subject.

Why is it useful?

Brainstorming is useful because it can help a group of people utilize its collective brainpower to generate many ideas in a short period of time.

It stimulates creativity and promotes involvement and participation.

When is it used?

It is used to help clarify mutual expectations and devise ground rules related to a team's way of operating.

How is it done?

- Identify a topic, problem, or issue, and make sure there is mutual understanding of the task and objective. Write the topic on a flip chart.
- Each person presents one idea going in sequence (round robin). If a person does not have an idea, pass and move on to the next person.
- All ideas are recorded on a flip chart.
- There is no evaluation or discussion during the session.
- Focus is on quantity of ideas, not the quality.
- When all ideas are exhausted, take a break. When you come back, people may have more ideas to add to the list.
- Keep the idea generation separate from the evaluation or analysis of ideas.

Brainstorming guidelines

- Generate as many ideas as possible.
- Encourage free-wheeling.
- No criticism is allowed, either positive or negative.
- Enable an equal opportunity to participate.
- Record all ideas.
- Let the ideas incubate.

During analysis, ideas should be evaluated, further analyzed, and refined prior to taking further action.

Fishbone diagram

What is it?

The fishbone diagram (also known as the cause and effect diagram (Exhibit 9.10)) is a technique to graphically identify and organize many possible causes of a problem (effect).

Why is it useful?

Fishbone diagrams help identify the most likely root causes of a problem. They can also help teach a team to reach a common understanding of the problem. This tool can help focus problem solving and reduce subjective decision-making.

When is it used?

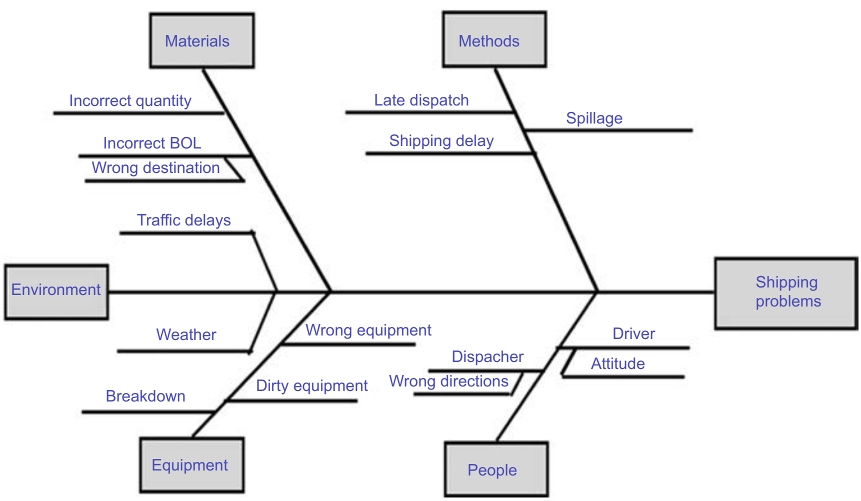
It is used when the need exists to display and explore many possible causes of a specific problem or condition. This diagram allows the team to systematically analyze cause and effect relationships. It can also help with the identification of root causes.

What does it look like?

Exhibit 9.10

*** Cause and effect diagram**

- * Allow team members to specify where ideas fit into the diagram
- * Clarify the meaning of each idea using the group to refine the ideas. For example:



Cause and effect

Fishbone considerations: When the entire occurrence has been charted out, the team is in a much better position to identify the major contributors to the failure/event.

You begin to identify and eliminate contributing factors such as the following:

- Manpower: operator errors
- Materials: component failures, expired materials, wrong materials
- Method: wrong steps in procedure
- Machine: wrong or lack of maintenance, out of calibration

By process of elimination you can get to the real cause (assign an M to an RCA team member).

Note: Sometimes events can be linked to a combination of contributors.

How is it done?

- Name the effect: determine the specific problem to be analyzed. Draw the diagram with a process arrow to the effect, and draw a box around it.
- Decide what the major categories of the causes are (e.g., people, machines, measurement, materials, methods, environment, and policies).
- Label categories important to your situation. Make it work for you.
- Brainstorm all possible causes, and label each cause under the appropriate category.
- Post the diagram where others can add causes to it (e.g., experts, affected people, and process owners).
- Analyze causes and eliminate trivial and/or frivolous ideas.
- Rank causes, and circle the most likely ones for further consideration and study.
- Investigate the circled causes. Use other techniques to gather data and prioritize findings.

Guidelines

- Try not to go beyond the span of control of the group.
- Promote participation by everyone concerned.
- Keep the chart up to date so it can be used throughout the improvement cycle.

People

- Was the document properly interpreted?
- Was the information properly disseminated?
- Did the recipient understand the information?

- Was the proper training to perform the task administered to the person?
- Was too much judgment required to perform the task?
- Were guidelines for judgment available?
- Did the environment influence the actions of the individual?
- Are there distractions in the workplace?
- Is fatigue a mitigating factor?
- How much experience does the individual have in performing this task?

Machines

- Was the correct tool used?
- Is the equipment affected by the environment?
- Is the equipment being properly maintained (i.e., daily/weekly/monthly preventive maintenance schedule)?
- Was the machine properly programmed?
- Are the tooling/fixtures adequate for the job?
- Does the machine have an adequate guard?
- Was the tooling used within its capabilities and limitations?
- Are all controls including emergency stop button clearly labeled and/or color coded or size differentiated?
- Is the machine the right application for the given job?

Measurement

- Does the gage have a valid calibration date?
- Was the proper gage used to measure the part, process, chemical, or compound?
- Was a gage capability study ever performed?
- Do measurements vary significantly from operator to operator?
- Do operators have a tough time using the prescribed gage?
- Is the gage fixture adequate?
- Does the gage have proper measurement resolution?
- Did the environment influence the measurements taken?

Material

- Is a Material Safety Data Sheet readily available?
- Was the material properly tested?
- Was the material substituted?
- Is the supplier's process defined and controlled?
- Were quality requirements adequate for part function?

- Was the material contaminated?
- Was the material handled properly (stored, dispensed, used, and disposed)?

Environment

- Is the process affected by temperature changes over the course of a day?
- Is the process affected by humidity, vibration, noise, or lighting?
- Does the process run in a controlled environment?

Methods

- Was the canister, barrel, etc., labeled properly?
- Were the workers trained properly in the procedure?
- Was the testing performed statistically significant?
- Have I tested for true root cause data?
- How many *if necessary* and *approximately* phrases are found in this process?
- Was this a process generated by an Integrated Product Development (IPD) Team?
- Was the IPD Team properly represented?
- Did the IPD Team employ design for environmental principles?
- Has a capability study ever been performed for this process?

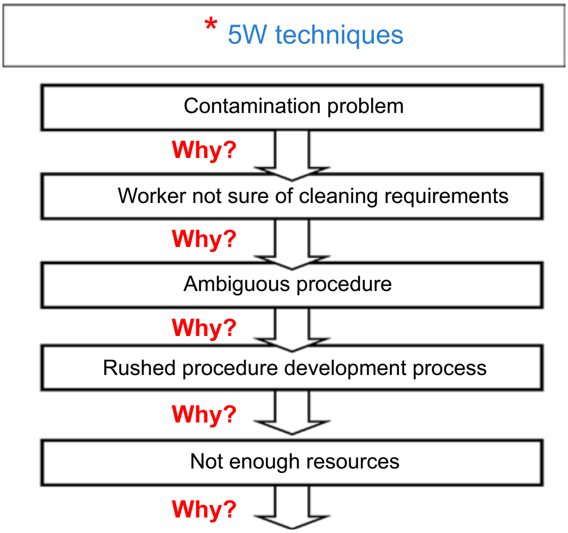
Methods

- Is the process under statistical process control?
- Are the work instructions clearly written?
- Are mistake-proofing devices/techniques employed?
- Are the work instructions complete?
- Is the tooling adequately designed and controlled?
- Is handling/packaging adequately specified?
- Was the process changed?
- Was the design changed?
- Was a process failure modes effects analysis ever performed?
- Was adequate sampling done?
- Are features of the process critical to safety clearly spelled out to the operator?

5W techniques or why diagram

Ask why at least five times! This is shown in Exhibit 9.11.

Exhibit 9.11

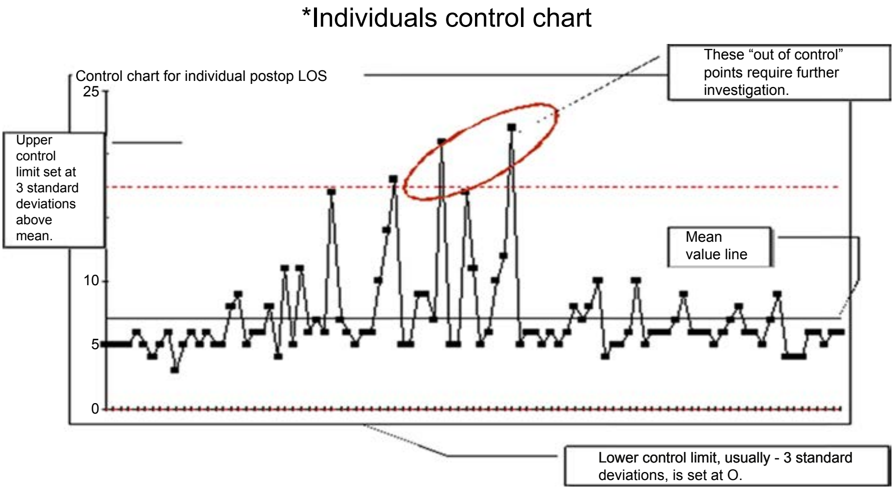


Control charts

Graphically display process stability and capability.

Identify significant events (called special cause variations) that require immediate management action. Identify trends before they become special causes (Exhibit 9.12).

Exhibit 9.12



Interpretation

- Any point outside the control limits is due to "special cause" variations and requires investigation.
- Individual points within the limits are a part of the normal (common cause) variation in the process. Improving them requires examination of the entire process.

Types of variation

Special cause: An event or run that statistically differs from the rest of the data. This means that the probability of the event or run occurring by chance is very small (usually <1%).

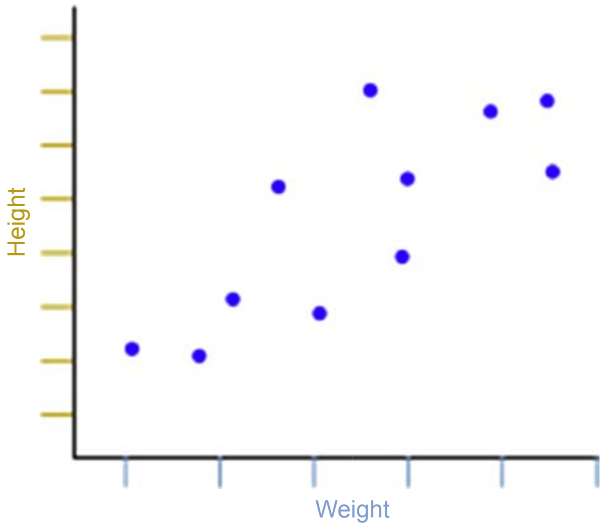
This type of variation is often called assignable cause because it is likely that only one of the myriad of causes impacting the process actually caused the event. Individual points within the limits are a part of the normal (common cause) variation in the process. Improving them requires examination of the entire process. Run chart trend analysis is also applicable (runs up/down).

Types of variation

Common cause: Other than the special cause events or runs process, data are random noise, and the signal of no one individual cause is discernible. When the process is operating at this level, it is stable and predictable. Any improvement efforts must address the entire causal structure (Exhibit 9.13).

Exhibit 9.13 Scatter plots: compare two values

Scatter plots



A scatter (XY) plot has points that show the relationship between two sets of data.

In this example, each dot shows one person's weight versus their height.

(The data is plotted on the graph as "Cartesian (x,y) coordinates")

Example

The local ice cream shop keeps track of how much ice cream they sell versus the noon temperature on that day. Here are their figures for the last 12 days (Exhibit 9.14).

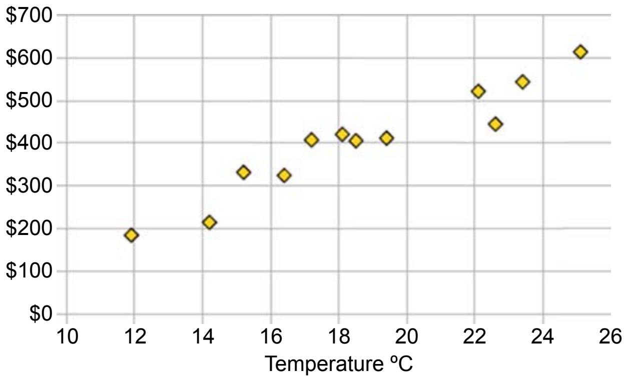
Exhibit 9.14 Ice cream sales versus temperature table

Ice cream sales versus temperature

Temperature (°C)	Ice cream sales
14.2	$215
16.4	$325
11.9	$185
15.2	$332
18.5	$406
22.1	$522
19.4	$412
25.1	$614
23.4	$544
18.1	$421
22.6	$445
17.2	$408

And here is the same data as a scatter plot (Exhibit 9.15).

Exhibit 9.15 Ice cream sales versus temperature scatter plot

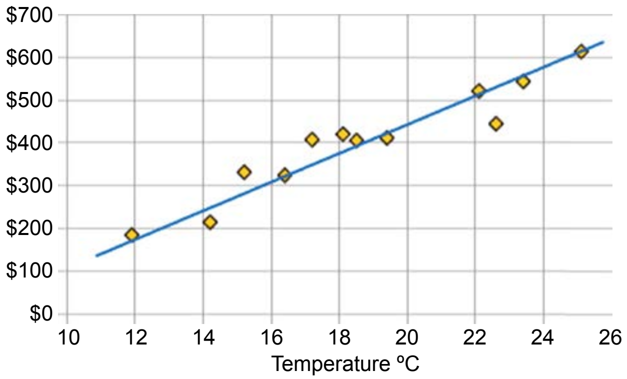


It is now easy to see that **warmer weather leads to more sales**, but the relationship is not perfect.

Line of best fit

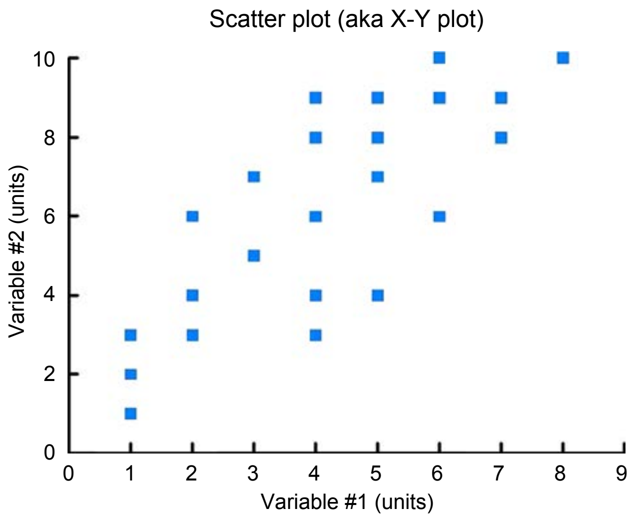
We can also draw a line of best fit (also called a trend line) on our scatter plot (Exhibits 9.16 and 9.17).

Exhibit 9.16 Ice cream sales versus temperature scatter plot with trend line



Source: https://www.mathsisfun.com/data/scatter-xy-plots.html

Exhibit 9.17



Text to describe the graph goes here (underneath graph).
For example to describe that variable 1 and variable 2 seem positively correlated because as one increases so does the other.

Check sheets can be used to gather and group data

Check sheets and check lists are the final major TQM tools. Check sheets are forms that gather data and allow users to easily analyze and interpret that data. The check sheet, however, is only meant to gather one type of data at a time, so these are really only good for data that is going to repeat often.

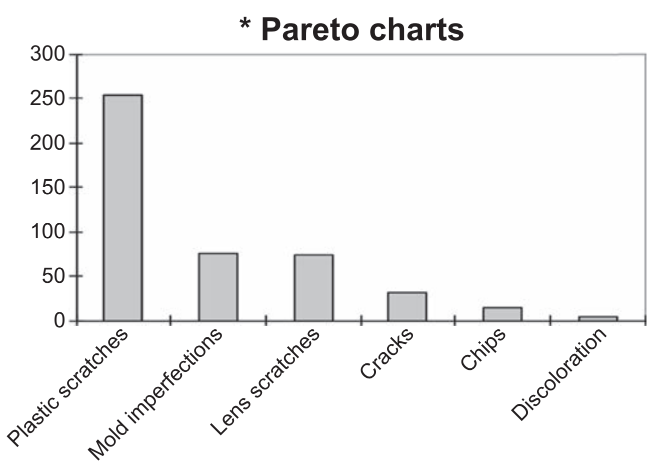
Check lists, on the other hand, are meant to deal with a specific problem (Exhibits 9.18 and 9.19).

Exhibit 9.18

Check sheets

Defect type	Nov. 18	Nov. 19	Nov. 20	Nov. 21	Nov. 22	Total freq.
Rust	III	I	III		II	9
Dents	~~IIII~~ II	IIII	III	~~IIII~~ II	III	24
Burs	~~IIII~~ II	III	III I	I	~~IIII~~	20
Scratches	I	III			I	5
Dings	~~IIII~~ III	~~IIII~~	~~IIII~~ III	~~IIII~~ ~~IIII~~ ~~IIII~~ II	~~IIII~~ ~~IIII~~ II	50

Exhibit 9.19 Pareto chart



Pareto analysis

Separating the significant few from the trivial many

Pareto analysis is based on the premise that 80% of problems are due to 20% of the possible causes.

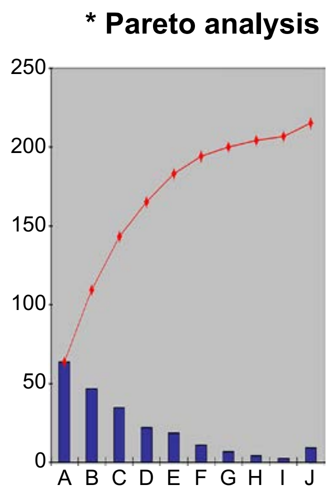
These 20% are the vital few problems a process improvement focuses on.

A Pareto analysis can also be described as a histogram **with two features added**. The first is the cumulative distribution curve. Second, the **vital few are identified** (Exhibit 9.20).

Exhibit 9.20

*** Example:**

*A - Broken tablets (52)
*B - Chipped tablets (46)
*C - Discolored (34)
*D - Spots on tablets (22)
*E - Embossing "FUZZY" (18)
*F - Bottle label skewed (11)
*G - Incorrect count (6)
*H - Lot # incomplete (4)
*I - Cap applied incorrectly (2)
*J - Others (9)



RCA

What is it? RCA is a methodology for finding and correcting the most important reasons for performance problems. In most cases, we have the tendency to blame things on humans and their errors. **Then, we need to ask the question: was the nonconformance caused by humans?** Human errors and human factors could include things such as traits, ability, knowledge, habits, and attitudes.

RCA differs from troubleshooting and problem solving in that these disciplines typically seek solutions to specific difficulties, whereas RCA is directed at underlying issues. As a process improvement tool, RCA seeks out unnecessary constraints as well as inadequate controls.

In risk management, it looks for both unrecognized hazards and broken or missing barriers. It helps target CAPA efforts at the points of most leverage. RCA is an essential ingredient in pointing change management efforts in the right direction. Finally, it is probably the only way to find the core issues contributing to your toughest problems, whether these problems are related to people, systems, or equipment.

The following are some problems that prevent good investigations and RCA:

- Crisis focus
- Wrong questions
- No time to find root causes
- Band-Aid approach (understand later)
- Symptom focus
- Blame (fear), only learn reactively
- Do not look for trends
- When all else fails: retrain
- Importance of the root cause

A standard process of the following:

- Identifying a problem
- Containing and analyzing the problem
- Defining the root cause
- Defining and implementing the actions required to eliminate the root cause
- Validating that the corrective action prevented recurrence of problem

In many cases, companies tend to blame everything on operators, and the most likely root cause is human error. Therefore, the number one corrective action is to retrain. However, if you have retrained several times for the same issue, then you are implying your training system is not effective. You are implying your CAPA system is not effective.

It is critical to determine the whys?

It is critical to determine why an event or failure occurred and be able to specify workable corrective measures that prevent future events. Understanding why an event occurred is the key to developing effective recommendations.

For example: If during a process an operator is instructed to perform an operation with a specific test solution and instead of the correct one the operator used the wrong solution, then we need to think what could be the cause of the error?

- The typical investigation would probably conclude that operator error was the cause.
  If this was the first result of the investigation and if the analysts stop here, they have not truly explored deeply enough the reasons for the error. The typical conclusion is to retrain!
  In the case where the operator used the wrong solution, we are likely to seek recommendations such as the following:
- Retrain the operator on the procedure.
  However, these types of recommendations do not truly prevent future occurrences. Therefore, you do not know what to do to prevent it from occurring again.

Mistakes do not just happen

Typically, mistakes do not just happen but can be traced to some well-defined causes. In the case of the operator error, we might ask the following:

- Was the procedure confusing?
- Were the solutions clearly labeled?

- Was the operator familiar with this particular task?
- Reviewing the options
- Reviewing these types of options and other questions will help determine why the error took place and what you can do to prevent recurrence.

In the case of the operator error, recommendations might include the following:

- Revising the procedure
- Performing procedure validation to ensure references to solutions match the testing solutions labels

But who is to blame? The *no blame* environment is critical. Most human errors are due to a process error. A sufficiently robust process can eliminate human errors. Placing blame does not correct a root cause situation.

- Is training appropriate and adequate?
- Is documentation available, correct, and clear?
- Are the right skill sets present?

Preventing human error

Why do humans make mistakes? How could you examine specific human errors to identify the conditions and situations that contributed to the mistakes? You will discover that most human mistakes are really caused by error-likely situations.

These error-likely situations typically stem from weaknesses in the policies/practices that influence how we select, train, communicate with, and design the workplace for workers. What are some practical methods to address the conditions and situations that contributed to the mistakes?

Error proofing: 5S methodology

- When trying to develop systems, questions to ask are how frequent and widespread. Is this the first time? (Who does not err?)
- Does the person make many errors?
- (If so, he or she is poorly placed, incapable, or poorly trained. A pattern of making errors demands the supervisor's attention to the person and to himself/herself.)
- Do others make similar errors?
- Does the person know he/she made a mistake?
- Does he/she know how to correct it?
- (If not, what does this say to the supervisor?)
- Was he/she trained or cautioned about the area of error?
- Does he/she do other things well?
- Plan to hear the employee's side.
- Don't rush in to accuse before hearing the accused.
- The employee's reasons for error might make sense if you hear them.
- Is the employee aware of the mistake?
- Under what conditions was the mistake made?

- Does he/she see the consequences of the error to the process, to the products, and the company?
- Follow-up.

Complimenting the employee when he/she does good work promotes mutual understanding.

Philosophy

It is good mental health to believe the following:

- All people make mistakes. Expect mistakes.
- People do not intend to make mistakes.
- People do not like to make mistakes.
- People want to make up for mistakes made.
- People want to learn from their mistakes.
- People improve performance after working out correction of mistakes (Exhibit 9.21).

Exhibit 9.21 Continuous improvement models: 5S

Sort (Seiri)	**Start by sorting the useful from the unnecessary.** The only things that should remain in a work area are the parts, tools, and instructions needed to do the job.
Set in order (Seiton)	**Everything has a place; everything is in its place.** This is also a good time for your team to create a visual scoreboard, floor paint, kanbans, and other visual controls.
Sweep & shine (Seiso)	**Do an initial spring cleaning.** Maybe painting, scouring, sweeping, washing, rinsing, or scrubbing is needed to make your workplace shine.
Standardize (Seiketsu)	In the standardize phase of lean 5S, routine cleaning becomes a way of life. **Preventive maintenance is routinely performed,** perhaps with planning and scheduling and some responsibilities done by your central maintenance department, and as much routine maintenance as possible performed by the people that know that work center better than anyone else.
Sustain (Shitsuke)	**Shitsuke is when 5S becomes a routine way of life.** Root causes are routinely identified and dealt with.

Continuous improvement models: 5S

- Sort: Get rid of clutter. Separate out what is needed for the operations.
- Set in order: Organize the work area. Make it easy to find what is needed.
- Shine: Clean the work area. Make it shine.
- Standardize: Establish schedules and methods of performing the cleaning and sorting.
- Sustain. Implement mechanisms to sustain the gains through involvement of people and integration into the performance measurement system, discipline, and recognition.

Human error assessment and reduction technique

Human error assessment and reduction technique (HEART) is a technique used in the field of human reliability assessment (HRA) for the purpose of evaluating the probability of a human error occurring throughout the completion of a specific task.

From such analyses, measures can then be taken to reduce the likelihood of errors occurring within a system and therefore lead to an improvement in the overall levels of safety.

There exist three primary reasons for conducting an HRA: error identification, error quantification, and error reduction.

As there exist a number of techniques used for such purposes, they can be split into one of two classifications: first-generation techniques and second-generation techniques.

First-generation techniques work on the basis of the simple dichotomy of fits/does not fit in the matching of the error situation in context with related error identification and quantification, and second-generation techniques are more theory based in their assessment and quantification of errors.

The HEART method is based upon the principle that every time a task is performed, there is a possibility of failure, and the probability of this is affected by one or more error-producing conditions, for instance:

- Distraction
- Tiredness
- Cramped conditions

Summary

- RCA is a method to focus our efforts on the true root causes of escapes, so that we truly prevent their reoccurrence.
- RCA helps us reduce turn backs and frustration, maintain customer satisfaction, and reduce costs significantly.
- Each problem is an opportunity. It contains the information needed to eliminate the problem. But to identify the root cause, we have to ask *why* over and over, until we reach it.

Exhibit 9.22 provides examples of is/is not tables that could also be used during the root cause investigation:

Exhibit 9.22

	Is	Verified	Is not	Verified	Data needed	Tools to collect or analyze
What	What specific object has the defect?		What similar objects could have the defect, but do not?			
	What is the specific defect?		What other defects could be seen, but are not?			
	What are the defect characteristics?		What could the characteristics be, but are not?			
	What product lots have the defect?		What product lots could have the defect, but do not?			
	What part lots are linked with the defect?		What part lots are not linked with the defect?			
	What processes should be investigated?		What processes are not under investigation?			
	What patterns are in the *what* data?		What patterns are not seen in the *what* data?			
Where	Where is the defective object observed geographically?		Where else could the defective object be observed geographically, but is not?			
	Where is the defect on the object?		Where else could it be on the object, but is not?			
	Where is the defect first seen in the process?		Where could it be first seen in the process, but is not?			
	Where else is the defect?		Where else could the defect be, but is not?			
	What patterns are in the *where* data?		What patterns are not seen in the *where* data?			

When	When was the defective object first observed?	When else could the defective object first been seen, but was not?
	What patterns are in the *when* data?	What patterns are not seen in the *when* data?
How much	How many objects have the defect?	How many objects could have the defect, but do not?
	What is the size of the defect?	What other size could it be, but is not?
	How many defects are on the object?	How many defects could be on object, but are not?
	What is the trend (stable, worse, better)?	What trends could have been seen, but have not?
	What patterns are in the *how much* data?	What patterns are not seen in the *how much* data?

Problem:

	Is	Verified	Is not	Verified	Differences	Changes
What						
Where						
When						
How much						

Problem:

	Is	Verified	Is not	Verified	Does not explain What *is*/ *is not* facts are not explained?	Assumptions What assumptions have to be made to explain the facts?	Verified
What							
Where							
When							
How much							

Part III: example of investigation tools for why diagrams and fault tree diagrams

Description of the issue/problem statement

The supplier management procedures do not clearly define acceptance criteria for supplier performance nor actions to be taken if the criteria are not met.

Containment/correction

To correct the issue, some immediate actions/corrections related to the supplier management were taken.

1. **Perform an audit on ABC supplier:** The audit of ABC supplier was performed by Quality representative from XYZ plant personnel (supplier evaluation 2014, but missed 2015 audit as required per SOP).

Investigation plan

The investigation plan consists of the following actions:

- Brainstorming to identify all potential root causes
- Using investigation tools such as the fishbone/Ishikawa diagram, 5W, or FTA to determine potential root causes
- Verifying the potential causes and identifying the causes that will be investigated in detail and addressed in the action plan

Investigation elements

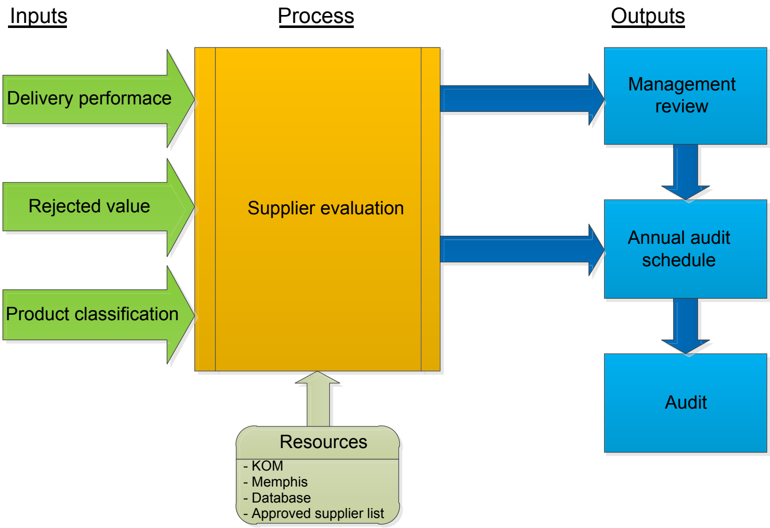
Brainstorming was performed the 26th of October.

Unfortunately, the fishbone/Ishikava diagram was not really applicable to the case.

For the investigation, the 5W method was used and clearly organized in FTA analysis, shown next.

When the process mapping was performed for the current process, it showed several details that needed to be taken into account to the current supplier management process, inputs, and outputs related from. Actions themselves are not mentioned in process mapping as long as they are described in a way as optional, and they are not strictly defined for exact rating after the evaluation. it not means that various actions are not applied after (Exhibit 9.23).

Exhibit 9.23



The current process of the supplier evaluation does not take into account primary information coming from "supplier selection and qualification" as the first step of the supplier management process. Either it does not take into account additional possible sources of supporting key indicators available or that can be provided by Quality, NCRs, SCARs, or it does not account for possible negative or positive outcomes from supplier audits.

Current product classification is defined in a way that all direct materials are classified as critical ones.

After the brainstorming, the team decides to split the main problem statement and investigate it in two issues:

1. Not clearly defined acceptance criteria
2. No actions to be taken if the criteria are not met

Part 1: acceptance criteria for supplier performance are not clearly defined

Why?

1.1 Primary definition wrong/not appropriate

Why?

1.1.1 Include only logistic figures (delivery performance, rejected value), missing other key indicators (SCAR, NCR, audit result)

Why?

1.1.1.1 Weak product classification (all the direct materials stated as critical, which cannot be true)

1.1.1.2 Supplier qualification not taken in account properly (part of this is to be an example audit at supplier)
1.1.1.3 Not centralized system for appropriate data collection
1.1.1.4 No cross-functional team at time of definition
Why?
1.1.1.4.1 Not accurate use/selection of possible QA input
Why?
1.1.1.4.1.1 Supplier management/evaluation defined only by logistics

Why?
1.1.2 No cross-functional team at time of definition
Why?
1.1.2.1 Not accurate use/selection of possible QA input
Why?
1.1.2.1.1 Supplier management/evaluation defined only by logistics
1.1.2.1.2 Lack of knowledge

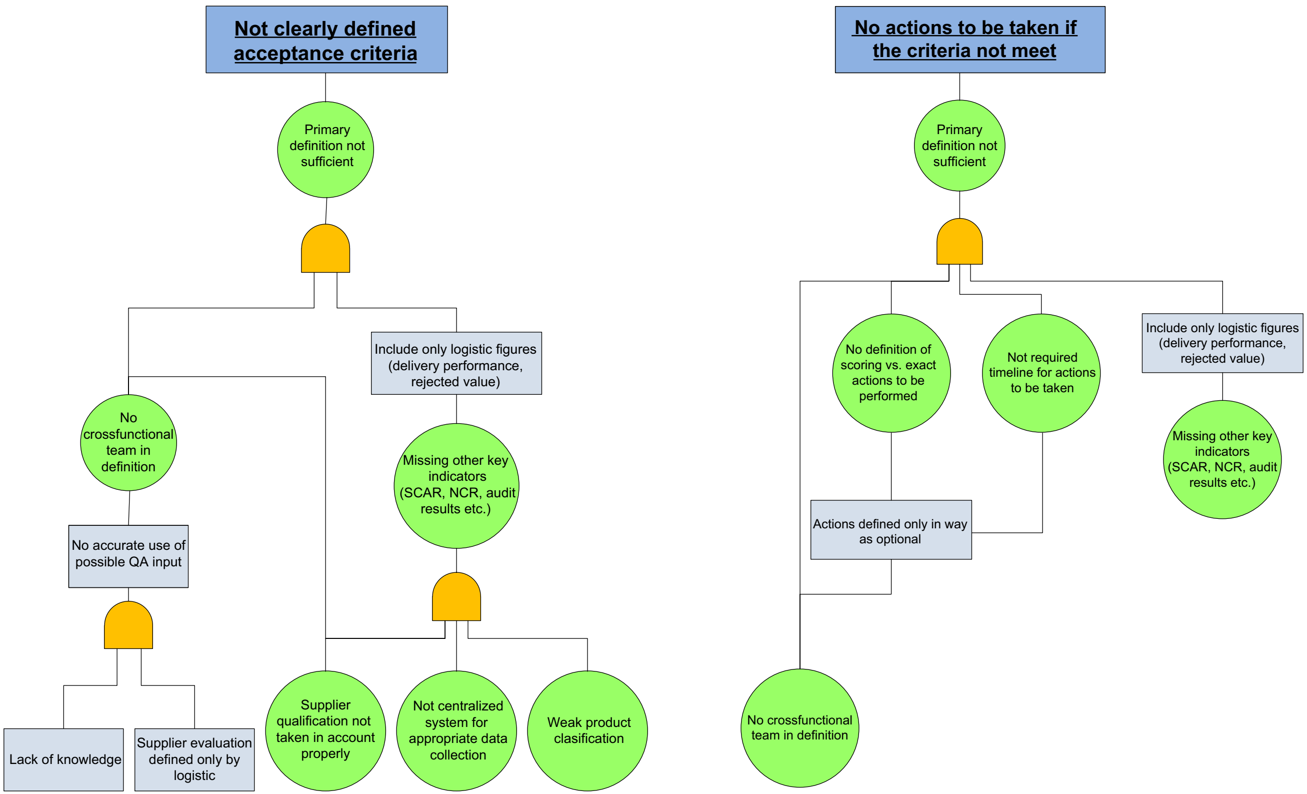
Part 2: do not define the actions to be taken if criteria are not met

Why?
1.1 Primary definition not sufficient
Why?
1.1.1 No definition scoring versus exact actions to be performed
Why?
1.1.1.1 Actions defined only in way as optional
Why?
1.1.1.1.1 No cross-functional team in definition

Why?
1.1.2 No required timeline for actions to be taken
Why?
1.1.2.1 Actions defined only in way as optional
Why?
1.1.2.1.1 No cross-functional team in definition

Why?
1.1.3. Criteria concentrated only on logistic figures, leads to current definition
Why?
1.1.3.1. Missing other key indicators that could also evoke specific/concrete actions
Why?
1.1.3.1.1 No cross-functional team in definition (Exhibit 9.24)

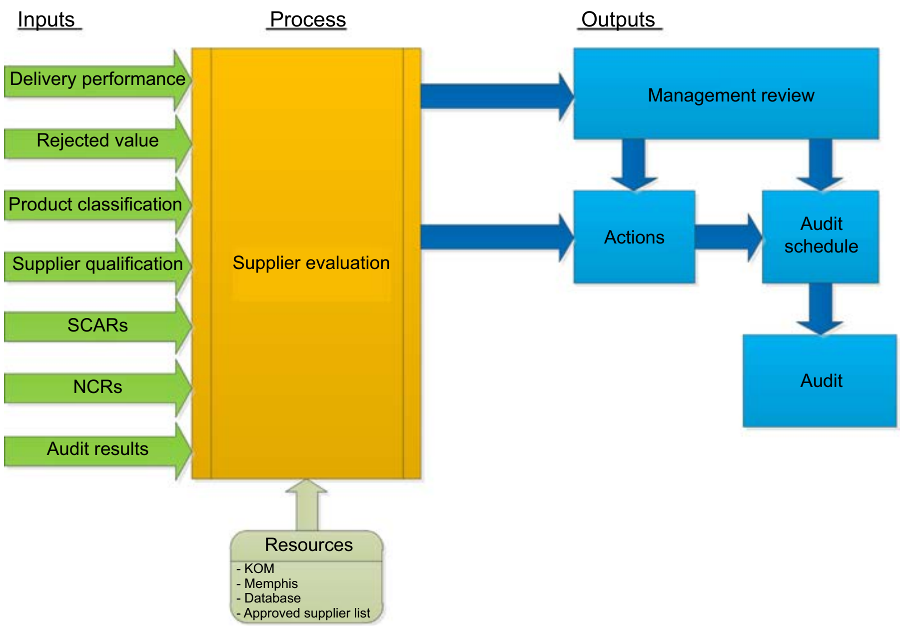
Exhibit 9.24


Not clearly defined acceptance criteria
Primary definition not sufficient
Include only logistic figures (delivery performance, rejected value)
No crossfunctional team in definition
Missing other key indicators (SCAR, NCR, audit results etc.)
No accurate use of possible QA input
Lack of knowledge
Supplier evaluation defined only by logistic
Supplier qualification not taken in account properly
Not centralized system for appropriate data collection
Weak product clasification
No actions to be taken if the criteria not meet
Primary definition not sufficient
No definition of scoring vs. exact actions to be performed
Not required timeline for actions to be taken
Include only logistic figures (delivery performance, rejected value)
Missing other key indicators (SCAR, NCR, audit results etc.)
Actions defined only in way as optional
No crossfunctional team in definition

Additional finding during investigation=>Current annual supplier evaluation seems to be not satisfactory; quarter base will better reflect actual situation/possible problems where needed to act.

Exhibit 9.25 shows a more efficient way of mapping the supplier management.

Exhibit 9.25



Summary of root/contributing causes

By brainstorming, 5W and FTA analysis have identified several root causes for the particular parts of the problem statement. As visible in the FTA analysis, the root causes are repeated in both parts of investigation. They are as follows:

- RC1. Primary definition of the supplier evaluation (supplier evaluation SOP) not sufficient
- RC2. Missing other key indicators (SCARs, NCRs, audit results) taken into consideration during supplier evaluation
- RC3. Weak product classification (procurement SOP), all direct materials defined as critical, without scaling of the criticality level
- RC4. Supplier qualification not taken into account properly, part of the supplier qualification is preliminary supplier audit that could be used as a good base to the later supplier evaluation
- RC5. No cross-functional team in definition, supplier evaluation defined from one-sided view
- RC6. No definition of the scoring versus exact actions to be performed/taken

- RC7. No required timeline for actions to be taken
- RC8. Not centralized system for appropriate data collection

Investigation and root cause conclusion

Potential root causes were identified during the investigation. All potential root causes will be addressed in CAPA plan.

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Step 7: corrective and preventive action plans

10

Completing corrective/preventive action plans

With the identification of the root cause, the next step is to develop an action plan. An action plan is completed to determine what will be done, who will do it, how it will be done, where it is going to be done, etc. Ensure that you have a list of things that are going to be implemented to allow for effective follow-up and confirmation of everything that is to occur.

An important part of CAPA is developing a list of actions that will need to be completed to address root causes. A corrective action(s)/preventive action(s) plan (please see Exhibit 10.1) can be used to review, evaluate, and document not only all actions related to corrections, corrective actions, and preventive actions, but also to document (if any) the impact of change to ensure that actions will not adversely affect other products, processes, or procedures and to ensure that the requirements for a change control record are in accordance with the change control procedure. Where applicable, the CAPA plan should include a reference to the change control number to provide linkage between the systems.

During the CAPA plan development, the organization should consider the effectiveness checks that will be required to ensure that the corrective action achieved the intended result of eliminating the identified issue/nonconformance.

The effectiveness check is not required to be comprehensive at this stage, but as a guide to show that the strategy and objective evidence required to establish effectiveness have been considered. The effectiveness check may evolve as the CAPA plan is implemented.

For investigations where a clear root cause(s) has been identified that requires a simple corrective action:

- Define a corrective action(s)/preventive action(s) plan using a table to track (please see Exhibit 10.1)
- Obtain QA review of proposed actions
- Initiate corrective action(s)/preventive action(s)

CAPA in the Pharmaceutical and Biotech Industries. http://dx.doi.org/10.1016/B978-1-907568-58-9.00010-2

For investigations where several root cause(s) have been identified and/or corrective action(s)/preventive action(s) are detailed and/or may impact other systems, processes, materials, or products:

- Define a corrective action/preventive action plan
- Obtain QA/CRB review prior to initiating corrective action(s)/preventive action(s). Note: The amount of detail required by the plan will be commensurate with the complexity of the correction, corrective action, or preventive action. Detailed plans must fully describe required actions and responsibilities, and timelines are required for corrective action or preventive action.

The organization should review the corrective action/preventive action plan to determine the following:

- If the proposed corrective action and/or preventive action will address the associated root cause
- If the CAPA plan provides sufficient detail of required actions, responsibilities, and realistic timescales

Identify corrective action and/or preventive action, where necessary, for issues that impact similar products, materials, equipment, processes, facilities, or systems at the site, and assign responsibilities accordingly. Any requests for changes to the approved corrective action and/or preventive action plans should be reviewed by Quality Assurance.

Exhibit 10.1 Corrective action/preventive action plan template

Corrective action/preventive action plan:

Root cause #	Action type: (C/CA/PA)	Action/task to be completed:	Action owner	Target completion date

Exhibit 10.2 shows examples of several corrective and preventive action plans and the linkage to each individual root cause that is being addressed:

Exhibit 10.2 CAPA plan (completed example)

CAPA Plan, Page _ of _

CAPA data base event # 1234	**CA/PA(s)#**: N/A	**Revision**: 2.0		**Date**: Jul 12, 2015	
Event owner:	Jane Smith	**CA/PA owner**:		John Doe	

Root Cause(s) to be addressed:

Root Causes

RC1. Missing other key indicators (SCARs, NCRs, Audit results) taken into consideration during supplier evaluation

RC2. Weak product and materials classification all direct materials defined as critical, without scaling of the criticality level

RC3. Supplier Qualification not taken in account properly – Result of possible audit during supplier qualification process not taken in account as a base for right supplier treatment and evaluation

RC4. Not centralized system for appropriate data collection – no local data collection on one place (server) from affected areas (logistic, purchasing, quality) which makes evaluations more appropriate

Contributing Causes

CC1. Primary definition of the supplier evaluation not adequate

CC2. No definition of the scoring vs. exact actions to be performed/taken

CC3. No required timeline for actions to be taken

CC4. Actions defined only in way as optional

Verify or validate the corrections, corrective and preventive action to ensure that such action is effective and does not adversely affect the finished device;

☐ **Correction** ☐ **Corrective Action** ☐ **Preventive Action**

CA/PA Owner Name	Job Title	Signature	Date
Jane Smith	QA Manager		

CAPA Plan, Page_ of _

Corrective action/preventive action plan:

Root cause #	Action/task to be completed:	Action type: (C/CA/PA)	Responsibility	Target date for completion	Comments/and impact assessment of the proposed change
RC1 CC1	Redefine supplier evaluation, supplier in procurement SOP, and supplier evaluation SOP from current process counting only received value and rejected value to the process that will include amount of the SCARs, NCRs, and also results of the supplier audits	CA # 1	Jane Smith John Doe		SOP XXX supplier evaluation, new effective version/no impact
RC1	In supplier evaluation SOP, define system of the scoring that will count and give appropriate ranking base on all criteria including newly implemented	CA # 2	Jane Smith John Doe		SOP XXX supplier evaluation, new effective version/no impact
RC1	Supplier evaluation has to be adjusted on quarter basis to reflect possible negative trends of the supplier	PA # 1	Jane Smith John Doe		SOP XXX supplier evaluation, new effective version/no impact
CC2 CC4	In supplier evaluation procedure, define what exact action to be taken versus achieved scoring	CA # 3	Jane Smith John Doe		SOP XXX supplier evaluation, new effective version/no impact

CAPA Plan, Page_ of _

Corrective action/preventive action plan:

Root cause #	Action/task to be completed:	Action type: (C/CA/PA)	Responsibility	Target date for completion	Comments/and impact assessment of the proposed change
CC3	In supplier evaluation procedure (XXX) define required timeline for specific action to be taken after the supplier evaluation	CA # 4	Jane Smith John Doe		SOP XXX supplier evaluation, new effective version/no impact
RC2	Redefine/readjust criticality level of the component for all direct materials	CA # 5	Jane Smith John Doe		SOP XXX product/ service categorization, new effective version/ no impact
RC2	Describe adjustment of the criticality level for new coming components	PA # 2	Jane Smith John Doe		SOP XXX product/ service categorization, new effective version/ no impact
RC3	Define exact system how to reflect supplier audit from phase of the supplier qualification to the supplier evaluation	CA # 6	Jane Smith John Doe		SOP XXX supplier evaluation, new effective version SOP XXX supplier qualification, new effective version/no impact
RC3	SOP for supplier audit revision	CA # 7	Jane Smith John Doe		SOP XXX supplier audit, new effective version/no impact
RC4	On local server (O:\ drive) create shared folder between logistics, purchasing and quality	CA # 11	Jane Smith John Doe		Folder map and appropriate templates/no impact
RC4	Define exact content and structure of created folder to ensure clear addressing and storing of the relevant data	CA # 12	Jane Smith John Doe		Folder map and appropriate templates/no impact

Note: All root causes must show a clear linkage to the corresponding corrective action. However, not all corrective action will result in a preventive action. If there is not applicable preventive action, then the organization should clearly document that no need for preventive action was necessary, and the rationale for not implementing preventive actions should be documented as shown in Exhibit 10.3 and Exhibit 10.4.

Exhibit 10.3 CAPA plan

Root cause #	Correction	Corrective action	Impact of CA	Preventive action
RC1	RC1-C1	RC1-CA1	CA1/no impact	RC1-PA1
RC1 = 2	RC2-C2	RC2-CA2	CA2/no impact	RC1 = 2-PA2

Exhibit 10.4 CAPA Plan—multiple corrective actions per root cause

Root cause #	Correction	Corrective action	Impact of CA	Preventive action
RC1	RC1-C1	RC1-CA1	CA1/no impact	RC1-PA1
RC1	None	RC1-CA2	CA2/no impact	RC1-PA not applicable

Exhibit 10.5 Corrective Action and Preventive Action (CAPA) Report

CAPA no:		**Rev.**		**Date CAPA initiated:**	04/30/2014
CAPA owner:				**CAPA owner signature:**	

Corrective and Preventive Action (CAPA) report number: ___________ ***Date***: __________

CAPA source (check source(s) and add applicable report number):

☐ CAPA _____________ ☐ Complaint _____________ ☐ Internal/external audit _____________

☐ Nonconforming product/process _________________ (Complete nonconforming product/process information below)

☐ Calibration _______________ ☐ Process failure ______________

☐ Supplier corrective action _______________________

☐ Installation ___________ ☐ Servicing _____________ ☐ Other ____________________________________

Are other procedures/products/processes affected ☐ No ☐ Yes (Document in report)

Description of issue – (Who, what, when, where, how) Please document as much information as possible.

Risk evaluation:

Immediate correction/containment of issue

CAPA initiation approvals

Quality assurance manager ____ Date: _______________________

Department manager ____ Date: _______________________

Department manager ____ Date: _______________________

(Add other managers as necessary)

Selection of CAPA team

CAPA team	**Name (print)**	**Title (print)**	**Signature**	**Date**
CAPA owner				
CAPA member				

QA management approval/date: ____________________________________

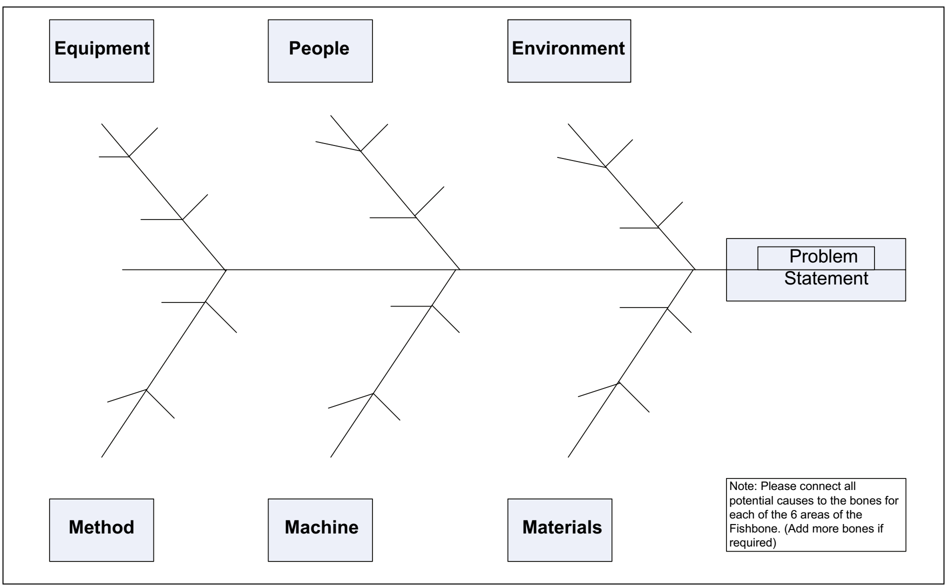
Section 4 – CAPA investigation/root cause analysis
Root or probable cause:
Check, use, complete, and attach required template(s) as applicable: ☐ **Form-XXX Root cause analysis (RCA) template** ☐ **Form-XXX Flowchart template** ☐ **Form-XXX Spider chart template** ☐ **Form-XXX Brainstorming template** ☐ **Form-XXX Is/is not template** ☐ **Form-XXX Check sheet template** ☐ **Form-XXX Histogram template** ☐ **Form-XXX Pareto chart template** ☐ **Form-XXX Scatter diagram template** ☐ **Form-XXX Fishbone template** ☐ **Form-XXX Five whys (5Ys) template** ☐ **Form-XXX Fault tree analysis (FTA) template** ☐ **Form-XXX Tree diagram template** ☐ **Form-XXX Force field analysis template**

Or use any of the following tools:

5 why analysis
(CAPA team must be assembled to perform the following 5 why analysis, and sign signature index sheet on completion)

Problem statement:		
	Question (why)	**Answer** (because)
1		
2		
3		
4		
5		

Ishikawa analysis
(CAPA team must be assembled to perform the following fishbone analysis, and sign signature index sheet on completion)



CAPA plan (add additional proposed CAPAs if required)			
	CA or PA?	CA/PA description	Proposed action date
1	CA ❐ PA ❐		
2	CA ❐ PA ❐		
3	CA ❐ PA ❐		
4	CA ❐ PA ❐		

CAPA plan approval

CAPA owner (lead): ______________________________ Date: __________
Department manager: ______________________________ Date: __________
(Add other managers as necessary)
Regulatory compliance management approval: ____________________ Date: __________

Corrective and/or preventive actions (add additional implemented CAPAs if required)					
	Implemented CA/PA (description)	Completion date	Responsible person(s)/ department(s)	Evidence (attach or reference)	CA or PA?
1					CA ❐ PA ❐
2					CA ❐ PA ❐
3					CA ❐ PA ❐
4					CA ❐ PA ❐

CAPA plan approval

CAPA owner (lead): ______________________________ Date: __________
Department manager: ______________________________ Date: __________
(Add other managers as necessary)
Regulatory compliance management approval: ____________________ Date: __________

Verification or validation of corrective and/or preventive action effectiveness (add additional CAPA information if required)							
	Implemented CA/PA (description)	Verification or validation of CAPA effectiveness	Completion date	Responsible person(s)/ department(s)	Evidence (attach or reference)	CA or PA?	Did CA/PA cause an adverse effect upon the product? (Yes or No) (Justify in writing if CAPA involved product)
1						CA ❐ PA ❐	☐ Yes ☐ No
2						CA ❐ PA ❐	☐ Yes ☐ No
3						CA ❐ PA ❐	☐ Yes ☐ No
4						CA ❐ PA ❐	☐ Yes ☐ No

Approval of verification or validation of CAPA effectiveness

CAPA manager: ______________________________ Date: ____________

CAPA closure

CAPA closure date: ______________
Quality assurance/ regulatory compliance: ____________________ Date: __________

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Step 8: implement and follow-up on action plans

11

Action plans

By using the results from the analysis, the optimum method for correcting the situation (or preventing a future occurrence) is determined and an action plan developed.

The plan should include, as appropriate, the items to be completed, document changes, any process, procedure, or system changes required, employee training, and any monitors or controls necessary to prevent the problem or a recurrence of the problem.

The action plan should also identify the person or persons responsible for completing each task.

Execution of the CAPA plan

The responsible person for each CAPA action must have completed their assigned task by the due date assigned. Objective evidence of the completion of each CAPA task must be attached to the CAPA record.

Example of objective evidence includes but is not limited to the following:

Training records
Validation reports
Change requests
Approved procedures with change history attached
Raw data with attached analysis

Reference any attachments that document the completion of the short-term corrective actions to its root cause.

When the CAPA plan has been completed in its entirety, all CAPA tasks should have been verified as complete by the investigation owner, and that person must verify that the necessary, predetermined evidence for task completion has been provided, including completed status updates and extension requests.

They also should verify where the training assessment indicates that training is required that the necessary training has been performed. CAPA verification should be performed by an independent party from the individual having completed the task.

Follow-up action plan

During and after the implementation of the plan, someone must follow-up on the work being performed. The action plan must be written so that independent follow-up may

CAPA in the Pharmaceutical and Biotech Industries. http://dx.doi.org/10.1016/B978-1-907568-58-9.00011-4

be completed by appropriate personnel. This plan will be challenged by regulatory agents both external and internal, so it should be precise and thorough. The follow-up will help confirm that the things that were supposed to have been done have actually occurred. This process will confirm, for example, that the follow-up was effective, that the procedures were changed, that people were trained, that equipment was updated, and that everything happened as specified in the plan. The CAPA plan must include follow-up.

As discussed before for each root cause from the investigation, the plan includes information that describes and justifies appropriate corrective actions and/or preventive actions, as applicable to correct and/or prevent reoccurrence or occurrence of the same deviation in the event being addressed and in other susceptible situations and processes.

Preventive action initiation follows the same path as a CAPA. An investigation outlining the situation and potential risks must be documented. Therefore, the organization must clearly link each action to its root cause, where applicable.

The CAPA plan follow-up should include documented evidence of the modifications to process, procedures, or systems needed to correct and prevent the identified nonconformance. Documents that required modification should be listed specifically, and the changes should be described in general terms.

Any changes in a process, procedure, or in a system must be described in enough detail so that it is clearly understood what is to be done. The expected outcome of these tasks should also be explained.

Where processes/methods or applications were modified, corresponding validation tasks must be included in the CAPA tasks to ensure that the modifications did not adversely affect the regulated product. In addition, documented and executed training activities where there were changes to processes or functions must be included.

Follow-up: a fundamental step in the CAPA process

- One of the most fundamental steps in the CAPA process is an evaluation of the actions that were taken. Several key questions must be answered:
- Have all recommended changes been completed and verified?
- The implementation and completion of all changes, controls, training, etc., must be verified. The evidence that this has been done must be recorded. Appropriate information should have been entered to document that all actions have been completed successfully.

Upon completion of each corrective action/preventive action

The organization should collate objective evidence to confirm that corrective/preventive action has been completed. This should include the notification to the CAPA coordinator/QA/corporate CAPA team, as applicable, of the completion of a corrective/preventive action.

Note: Objective evidence may be records, forms, procedures, or reports.

The review should include provided objective evidence to ensure that sufficient information is available to show that the action has been completed in accordance with agreed CAPA plans.

If sufficient objective evidence is available to show that the CAPA has been completed, the CAPA should be updated to include all details in paper or electronic format, as well as providing updates to the CAPA board team and/or any associated CAPA matrices.

If insufficient objective evidence has been provided, The CAPA owner may need to request additional information to determine if CAPA was effective and only lacking information or not effective. Once this is determined, the CAPA board team should be notified so that management is informed that the CAPA may need some additional investigation so that resources can be allocated accordingly.

CAPA and change control

Changes resulting from CAPAs should be documented through a change control process. This would ensure that all actions resulting from the investigation follow the change control procedure that would include all the details and the management of modifications and/or revisions to be made on manufacturing processes, production, testing and utilities equipment, equipment operating parameters, facilities, processes parameters, raw materials and process components specifications, analytical and microbiological methods, or computer software to assure that the validated state of equipment/process is maintained.

The objective is to ensure that all proposed modifications to a system/process are properly reviewed and to provide a mechanism for review and approval of results after the work is completed.

The change control procedure should include the evaluation and documentation of the change for all critical systems, processes, equipment, and instruments used to support production and product specifications. This procedure shall be used when any critical system undergoes one or more of the following changes on either a permanent or temporary basis:

1. Hardware modifications or parts replacements
2. Software modifications/revision
3. Process changes, or any other situation or event that may affect the validation status of a system
4. Changes to equipment/process validated parameters (including changes in parameter target values, parameter ranges, and equipment/instrument configuration settings)
5. Changes to raw materials/components specifications and/or procedures
6. Changes to product specifications

Change control process

A **change control procedure** should define the process for controlling changes that involve existing marketed products and device master record or drug master file documentation that includes products, processes, methods, equipment, packaging, and specifications, and changes to Quality Management System processes and documents.

The main purpose of the change control process is to ensure that any planned introduction, alteration, modification, replacement, and/or elimination of anything associated with the manufacture, processing, packing, testing, or holding of a medical device product post-design launch or any planned change within the Quality Management System has no deleterious impact on product safety, quality, intended use, or efficacy throughout product shelf-life.

A well-established change control process will help to ensure that changes to policies, standard operating procedures, work instructions, technical documents, and business documents that are progressed according to a change control procedure and undergo evaluation of any technical change as part of a governing change control record will be linked to the CAPA record.

This process will also help to ensure that both permanent and temporary changes are the following:

- Justified and documented
- A state of validation is maintained
- Maintain compliance with Good Manufacturing Practice and regulatory requirements
- Evaluated and approved by qualified individuals within the organization
- Supported by formal documentation, i.e., testing and acceptance criteria

Change request (CR) description

Typically a CR form is completed to describe required changes. This form should be completed as is explained in the next section of this document and should contain the following:

- A **change number** to manage the change
- The **date**
- A **description of the proposed change**. The change should be clearly detailed, specifying if it is due to new equipment and if the change is permanent or temporary. For temporary changes, the period of time or lots for which the change applies should be defined; a protocol describing and classifying the change may be attached to the CR.
- The **reason for change** should be clearly explained.

Classification of the change

To review the change from the point of view of the end user, a classification of the change should be done. The following criteria should be applied to classify the change:

- **Minor change:** Changes that are fairly minor and considered unlikely to affect the product's established specifications. Such changes should be documented but notification to the customer is not necessary.
- **Moderate change:** The impact of the change should be evaluated to determine its potential impact of the product functionality. Notification of these types of changes to the customer is strongly suggested. However, preapproval by the customer is normally not needed unless it is shown that functionality is affected.

- **Major change:** These changes are always significant. Unless there is sound basis for concluding the change does not impact product functionality, notification is required. Shipment of the changed product to the customer should not occur without consent of the customer.

In addition, an **impact analysis (IA)** should be completed for all kind of changes. An IA form should be attached to the CR and completed to classify the change.

- After performing an IA, an **implementation plan worksheet (IPW)** could also be required since it would confirm that all needed implementation was considered, documented, and the plan was used to confirm resources and tasks needed for implementation and follow-up of all activities.
- The IA and IPW should be included in the CR form.

IA form description

This form should be completed to evaluate and classify the impact of the change. It is typically divided into four sections.

- **Section A:** The primary department impacted by the change is identified, and the change proposed is described.
- **Section B:** The impact of the change in documentation, transactions, and specified processes is evaluated.
- **Section C:** It is evaluated if the change affects other equipment, systems, or interfaces with other systems, physical security, and the customer.
- **Section D:** A summary risk assessment analyzing Sections A, B, and C is performed, and additional information is included.

After preparation, this IA should be reviewed and approved.

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Step 9: verification of effectiveness

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Verification/effectiveness of the actions

Another important aspect of any CAPA action is to make sure that the actions taken were effective. A thorough evaluation must be done to make sure that the root cause of the problem has been solved, that any resulting secondary situations have been corrected, that proper controls have been established, and that adequate monitoring of the situation is in place.

This evaluation must also include an investigation to determine if the actions taken could result in any other adverse effects. This investigation and the results should be documented. The following is an example of a verification of effectiveness plan that resulted from an FDA inspection finding/observation noted in a the FDA's 483 form.

Closely on the heels of the follow-up or perhaps at the same time, the verification of the effectiveness of the corrective action will be conducted. In step 7, the follow-up confirmed that what was supposed to occur actually happened. The verification of the effectiveness of the action plan will be the crucial test and the culmination of the previous eight steps.

At this point, we want to make sure that what has been implemented as a corrective action has actually "cured" the problem. We must verify that our action plan has effectively eliminated the problem. If that is so, then we can implement it in other systems as a plan of preventive action. This will become the preventive action that we want to implement at a later time.

If we find that the chosen action has not cured the problem or has addressed only part of the problem, then we must go back through the program steps and either reanalyze the data (step 4) or perhaps get further data (step 2) until we discover the actual root cause or total root cause or causes (step 6). Or, we may only have to go back a few steps to the implementation of the action plan (step 7) to discover that there was a flaw in the way our solution was applied. We must backtrack as far as necessary along the process to discover the flaw and correct it—even if that means restating the problem (step 1)—to find the correct root cause (step 4) and have a truly effective action plan (step 5).

How to verify effectiveness

How do we evaluate the effectiveness of an action plan? Whether our activities are preventive or corrective, we want to make sure that we monitor the effectiveness of the time we spend performing them. Look at your corrective actions. What is the

CAPA in the Pharmaceutical and Biotech Industries. http://dx.doi.org/10.1016/B978-1-907568-58-9.00012-6

corrective action plan? Who is going to monitor whether the change, in fact, worked? Are they going to monitor a piece of equipment over time? Are they going to monitor an employee's performance over time? Define how you will monitor effectiveness, whether it is going to be over a period of time, during the next audit, or the next time you look at the system.

Specifically define how you are going to be completing the monitoring. Document what is to be done. Document how you will evaluate whether the corrective action plan actually works. Then communicate these activities to the responsible folks who have to implement them. Tell management that the actions worked. You have dealt with the problem effectively, and you have prevented this issue from recurring. Because of the monitoring and verification you performed, you now have documented evidence of your successful activities.

CAPA verification of effectiveness plan

The purpose of a plan is to provide the reader with an example verification of effectiveness protocol that also includes valid statistical rationale for the sampling of records needed to show that the corrective actions were effective and to identify and document the verification of effectiveness (VOE) plan to verify the effectiveness of the corrective actions taken as part of **CAPA CA-XYZ**. Successful execution of this plan should demonstrate that the corrective actions effectively addressed or mitigated the root causes identified in the CAPA record. The following should provide a step-by-step outline of what is needed to complete a VOE plan for both corrective actions and preventive actions:

First, you will need to clearly describe the problem statement. For example, *corrective actions have not been verified or validated to ensure that the actions taken are effective, are clearly linked to and address root cause, and do not adversely affect the finished device*.

Assign responsibilities:

- **CAPA owner:** Leads the CAPA Team to complete the CAPA
- **CAPA engineer:** Provides support for CAPA activities, serves as CAPA element SME
- **VOE auditor:** Verifies the effectiveness of the actions taken to address the issue

Verification of effectiveness prerequisites

The following prerequisites should be completed prior to initiating VOE activities:

CAPA Record: At the time of recording of this VOE protocol, all action items are completed with supporting objective evidence.

Root Cause(s): The root cause for the issue of corrective actions will be verified or validated to ensure that the actions taken are effective, are clearly linked to and address root cause, and do not adversely affect the finished device. They have been attributed to the following:

RC1: Procedure ABC, rev 1, effective date December 1, 2014, "Root Cause Analysis" was not in place at the time the CAPA was documented; Procedure XYZ, rev 2, and effective date October 2, 2014, "Corrective & Preventive Action System" does not adequately reference tools to use for root cause investigation.
RC2: Procedure XYZ, rev 2, effective date October 2, 2014, "Corrective & Preventive Action System" does not adequately reference procedure XYZ, rev 2, effective date September 3, 2015, "Verification of Effectiveness Planning."
RC3: Procedure XYZ, rev 2, effective date October 2, 2014, "Corrective & Preventive Action System" does not adequately differentiate between immediate and time-based verification methods.

Evaluation justification and VOE acceptance criteria

Functional area(s) and specific individuals to perform VOE:

VOE audit to be performed by Quality Assurance.
The specific individual performing the audit should be qualified as an Auditor or Lead Auditor per Internal Audit Program.

Example of tasks to be performed for determining VOE:

To perform the VOE, a sample of corrective actions should be reviewed against the appropriateness of root cause determination. Corrective action records should be reviewed to determine if root cause determination was appropriate to the issue/problem statement identified in the corrective action record.
Corrective actions must be assessed for appropriateness before implementation. Corrective action records should be reviewed to determine if the corrective actions in the corrective action record were assessed for appropriateness before implementation (verified for effectiveness) and evaluated for adverse effects.
Data should be collected using the data sheet in Exhibit 12.2 of this protocol.
In the event that any VOE plan deviations arise, the deviations should be documented through a revision to the VOE protocol, and any discrepancies documented during the execution of the VOE plan should be documented in the VOE report.

Methods of data collection:

Closed corrective action records should be reviewed from the CAPA database for both the site. Corrective action records that have been administratively closed to correction activities are excluded from this review.

Methods of analysis and acceptance criteria:

Records should be sampled for each of the above three criteria and should be determined to either pass or fail. If the number of records sampled meets the acceptance number for the binomial sampling selected for pass/fail criteria, then the VOE should be determined to pass requirements. If the number of records sampled meets the reject number for the binomial sampling selected for pass/fail criteria, then the VOE should be determined to fail requirements.

Statistical sample size:

The VOE should be executed using a sampling strategy, for example (Exhibit 12.1):

Exhibit 12.1 A 95% confidence, with a 95% probability of conformance, with $n = 59$ samples, accept with 0 significant nonconformities, reject with one significant nonconformities

Root cause	VOE method	Sample size and acceptance	Justification
RC1: ABC, "root cause analysis" was not in place at the time the CAPA was documented; procedure XYZ, " corrective and preventive action system" does not adequately reference tools to use for root cause investigation.	Review of CA records closed 6 months after implementation of ABC SOP updates for: Root cause determination was appropriate to the issue/ problem statement identified in the CA record.	$n = 59$ records, acc = 0, rej = 1 If $n < 59$, 100% of records, acc = 0, rej = 1	Binomial sampling per 001.01, data analysis for 95% confidence, 95% probability of conformance
RC2: Procedure XYZ does not adequately reference procedure 123, "verification of effectiveness planning."	Review of CA records closed 6 months after implementation of XYZ updates for: Corrective actions in the CA record were assessed for appropriateness before implementation (verified for effectiveness) and evaluated for adverse effects.	$n = 59$ records, acc = 0, rej = 1 If $n < 59$, 100% of records, acc = 0, rej = 1	Binomial sampling per 001.01, data analysis for 95% confidence, 95% probability of conformance
RC3: Procedure XYZ "corrective and preventive action system" does not adequately differentiate between immediate and time-based verification methods.	Review of CA records closed 6 months after implementation of XYZ updates for: Corrective actions in the CA record were assessed for appropriateness before implementation (verified for effectiveness) and evaluated for adverse effects.	$n = 59$ records, acc = 0, rej = 1 If $n < 59$, 100% of records, acc = 0, rej = 1	Binomial sampling per 001.01, data analysis for 95% confidence, 95% probability of conformance

Time interval:
The time frame for performing a VOE should be established up front. For example, this VOE protocol is 6 months after implementation of the changes according to approved CAPA plan.
Verification of adverse effect to product:
As required by 820.100, CAPA records should be reviewed to determine if the corrective actions in the corrective action or preventive action record were assessed for appropriateness before implementation (verified for effectiveness) and evaluated for adverse effects.

Finally, a completion due date needs to be documented and referenced, as well as the time frame justification.

Exhibit 12.2 Data collection sheet

ATTACHMENT 1 – DATA COLLECTION SHEET

Questions:

(One Questionnaire Per CA Record)

Is the root cause determination appropriate to the issue/problem statement identified in the CA record? (YES) (NO) If No please explain.

____

____

____

____

Were the corrective actions in the CA record assessed for appropriateness before implementation and evaluated for adverse effects? (YES) (NO) If No please explain.

____

____

____

____

CA Record Number: ____________________

Verification of Effectiveness

Results Recorded by: ____ Date: ______________

The following shows examples of several VOE checks, which are linked to the initial CAPA plans as well as to each individual root cause that is being addressed (Exhibits 12.3–12.6):

Exhibit 12.3 Example of a VOE check

CAPA plan		Page_ of _	
CAPA database event #: 1234	CA/PA(s) #: N/A	Revision: 2.0	Date: July 12, 2015
Event owner:	Jane Smith	CA/PA owner:	John Doe

Root Cause(s) to be addressed:

Root Causes

RC1. Missing other key indicators (SCARs, NCRs, Audit results) taken into consideration during supplier evaluation

RC2. Weak product and materials classification all direct materials defined as critical, without scaling of the criticality level

RC3. Supplier Qualification not taken in account properly – Result of possible audit during supplier qualification process not taken in account as a base for right supplier treatment and evaluation

RC4. No cross-functional team in definition, supplier evaluation defined from one sided view, only by logistic

RC5. Lack of knowledge and experiences with supplier treatment adjustment

RC6. Not centralized system for appropriate data collection – no local data collection on one place (server) from affected areas (logistic, purchasing, quality) which makes evaluations more appropriate

Contributing Causes

CC1. Primary definition of the supplier evaluation not adequate

CC2. No definition of the scoring vs. exact actions to be performed/taken

CC3. No required timeline for actions to be taken

CC4. Actions defined only in way as optional

Verify or validate the corrections, corrective and preventive action to ensure that such action is effective and does not adversely affect the finished device;

☐ **Correction** ☐ **Corrective Action** ☐ **Preventive Action**

CA/PA Owner Name	Job Title	Signature	Date
Jane Smith	QA Manager		

Actions Required:

☒ **Correction** ☒ **Corrective Action** ☐ **Preventive Action**

Contributors: ☐ *N/A for simple corrective actions*

Name:	Job Title:	Location/Site:
Jane Smith	QA Manager	Manufacturing site a
John doe	Logistic Manager	Manufacturing site a

Exhibit 12.4 CAPA plan

Corrective action/preventive action plan

Root cause #	Action/task to be completed	Action type (C/CA/PA)	Responsibility	Target date for completion	Objective evidence
RC1 CC1	Redefine supplier evaluation (G803005), from current process counting only with received value and rejected value to the process that will include amount of the SCARs, NCRs, and also results of the supplier audits	CA # 1	Jane Smith John Doe		SOP XYZ supplier evaluation, new effective version
RC1	In SOP XYZ, define system of the scoring that will count and give appropriate ranking based on all criteria, including new implemented	CA # 2	Jane Smith John Doe		SOP XYZ supplier evaluation, new effective version
RC1	Supplier evaluation has to be adjusted on quarterly basis, to reflect possible negative trends of the supplier	PA # 1	Jane Smith John Doe		SOP XYZ supplier evaluation, new effective version
CC2 CC4	In supplier evaluation procedure, define what exact action to be taken vs. achieved scoring	CA # 3	Jane Smith John Doe		G803005 supplier evaluation, new effective version
CC3	In supplier evaluation procedure (XYZ), define required timeline for specific action to be taken after the supplier evaluation	CA # 4	Jane Smith John Doe		SOP XYZ supplier evaluation, new effective version
RC2	Redefine/readjust criticality level of the component for all direct materials	CA # 5	Jane Smith John Doe		SOP XYZ product/service categorization, new effective version

(Continued)

Corrective action/preventive action plan

Root cause #	Action/task to be completed	Action type (C/CA/PA)	Responsibility	Target date for completion	Objective evidence
RC2	Describe adjustment of the criticality level for new coming components	PA # 2	Jane Smith John Doe		SOP XYZ product/service categorization, new effective version
RC3	Define exact system how to reflect supplier audit from phase of the supplier qualification to the supplier evaluation	CA # 6	Jane Smith John Doe		SOP XYZ supplier evaluation, new effective version SOP XYZ supplier qualification, new effective version
RC3	SOP for supplier audit revision	CA # 7	Jane Smith John Doe		SOP XYZ supplier audit, new effective version
RC4	All new definitions to be done with involvement of all departments, cross-functional definition by Logistic, Purchasing, Quality department	CA # 8	Jane Smith John Doe		Attendance evidence
RC5	Training for supplier management (e.g., supplier auditing)	CA # 9	Jane Smith John Doe		Training records and certificate
RC5	Implement new position SQA (Supplier Quality Assurance)	CA # 10	Jane Smith John doe		Job description and organization chart to contain SQA position
RC6	On local server (O:\ drive), create shared folder between Logistics, Purchasing, and Quality	CA # 11	Jane Smith John Doe		Folder map and appropriate templates
RC6	Define exact content and structure of created folder to ensure clear addressing and storing of the relevant data	CA # 12	Jane Smith John Doe		Folder map and appropriate templates

Exhibit 12.5 Effectiveness criteria

Proposed effectiveness criteria (corrective actions only)

	Measurement	
CA/PA #	**What will be measured**	**How will it be measured**
CA # 1, 2, 3, 4, 6 PA # 1	SOP XYZ supplier evaluation, new effective version	Verify missing key indicators are taken into consideration by independent audit
CA # 5 PA # 2	SOP XYZ product/service categorization, new effective version	Verify scaling of criticality levels for random materials by independent audit
CA # 6	SOP XYZ supplier qualification, new effective version	Verify if audit(s) were performed based on right supplier treatment and evaluation
CA # 7	SOP XYZ supplier audit, new effective version	Verify if audit(s) were performed based on right supplier treatment and evaluation
CA # 8	Attendance evidence	Verify if all required departments are present during supplier evaluations (signatures)
CA # 9	Training records and certificate	Test for personnel performing supplier qualification
CA # 10	Job description and organization chart for SQA	Verification of organization chart and presence of job description for SQA
CA # 11, 12	Folder map	Verification of folder map presence

CAPA plan, page_ of _

Product/process/procedural impact/validation requirements/change control

There is no impact to products or manufacturing processes as a result of the corrective action proposed in this plan. The corrective actions proposed pertain to quality system processes and do not have direct impact on existing product.

Signatures

CA/PA owner name	**Job title**	**Signature**	**Date**
Jane Smith	QA manager		
Quality name	**Job title**	**Signature**	**Date**
John Doe	Quality supervisor		

Exhibit 12.6 Effectiveness checks

Effectiveness checks

CAPA data base event #: 1234	**CA/PA(s) #**: N/A	**Revision**: 2.0	**Date**: July12, 2014
Event owner:		**CA/PA owner**:	
Target completion date:			

Root cause(s) addressed

RC1. Missing other key indicators (SCARs, NCRs, audit results) taken into consideration during supplier evaluation
RC2. Weak product classification (SOP ABC-123.), all direct materials defined as critical, without scaling of the criticality level
RC3. Supplier qualification not taken into account properly—result of possible audit during supplier qualification process not taken into account as a base for right supplier treatment and evaluation
RC4. No cross-functional team in definition, supplier evaluation defined from one sided view, only by logistic
RC5. Lack of knowledge and experiences with supplier treatment adjustment
RC6. Not centralized system for appropriate

include rationale for statistical sample size

Requirements

	Metric/data/area reviewed	**Measurement criteria**	**Acceptance criteria**	**Results**	**Objective evidence**
1	An independent audit of following procedure ABC-123	Confirm that key indicators (SCARs, NCRs, audit results) taken into consideration during supplier evaluation—59 supplier files to be reviewed			
2	An independent audit of following procedure ABC-123	Confirm that product classification (SOP ABC-123) all direct materials are now defined with the scaling of the criticality level—80 supplier files to be reviewed			
3	An independent audit of following procedure ABC-124	Resulting supplier audit evaluated and results of evaluation used during supplier qualification process			

Requirements

	Metric/data/area reviewed	**Measurement criteria**	**Acceptance criteria**	**Results**	**Objective evidence**
4	An independent audit of following procedure ABC-125	Confirm cross-functional team in definition, supplier evaluation by logistic and QA in new SOP			
5	Verification of attendance (signatures)	Confirm cross-functional team attendance for Logistics and QA per new SOP			
6	Verification of training records and certificates	Review of latest SOP revisions training records and track of knowledge and experiences with supplier treatment adjustment			
7	Verification of organization chart and presence of job description for SQA	Presence of job description for SQA			
8	Verification of folder map presence	Confirm centralized system for metrics storage of data			

Effectiveness check performed by

Name, title	**Signature**	**Date**
Bobby Brown		

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Results/Conclusions

Was Acceptance Criteria Met?

☐ **Yes**

☐ **No - Describe acceptance criteria that was not met:**

If no, what additional actions will be taken?

Approval of effectiveness determination results

Name, title	**Signature**	**Date**
Event owner:		
CRB representative:		

Conclusion

Effectiveness check assessment

The effectiveness assessment person or CAPA owner should be responsible for executing the effectiveness assessment in accordance with the approved effectiveness check plan.

They must ensure that the objective evidence satisfies the CAPA effectiveness acceptance criteria, demonstrating that the executed CAPA plan was effective in resolving the root cause of the nonconformance or will indeed prevent occurrence of the potential nonconformance.

Examples of objective evidence include but are not limited to the following:

- Raw and summary data of statistically relevant related customer complaints on the specified product demonstrating no incidents in the field
- Raw and summary statistically relevant OOS or NCR data indicating no issues with the materials
- Raw and summary statistically relevant data of a batch record review indicating no issues with the production, testing, or release of the materials

Objective results of the effectiveness assessment should be attached to the effectiveness check record to substantiate CAPA effectiveness. If the effectiveness assessment fails, this must be documented in the effectiveness check summary for subsequent QA rejection.

Upon completion of successful effectiveness check assessments, the record should be forwarded to QA for final approval.

Final approval

As part of approval it is the responsibility of ALL parties to ensure that the following criteria have been met:

Were all of the objectives of the CAPA plan met?

Have all of the changes been completed and verified?

Have appropriate communications (through change control) and necessary training been implemented?

Has it been demonstrated that the executed corrective action plan does not have any adverse effects on the product or ancillary processes?

If the effectiveness assessment has been successful, and the above criteria have been met, QA should approve the record and all associated records will be closed.

If the effectiveness assessment proves that the implemented CAPA has been ineffective in resolving the root cause, QA should open a new investigation record or reopen the existing investigation. By this time, if we followed the nine-step process, the effectiveness check should be easy to complete, and the CAPA could be closed and recurrence of initial failure causes will no longer be an issue.

Examples of procedures

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1. Control of nonconforming product
2. Out of specification (OOS) procedure
3. Corrective and preventive action (CAPA) system
4. FMEA procedure
5. Root cause analysis (RCA) standard operating procedure (SOP)
6. Quality systems data analysis

Procedure example #1:
SOP: control of nonconforming product

1. Purpose

This procedure provides the general requirements for controlling nonconforming products and materials. The requirements include the documentation, identification, segregation, evaluation, and disposition of nonconforming products and materials.

2. Scope

This procedure applies to G×P materials (including finished devices, in-process goods, raw materials, returned goods, and product samples) impacted by a nonconformance.

The investigation and corrective actions associated with product/process nonconformances, OOS, and supplier nonconformities will be addressed per the following procedures listed in the reference section:

3. References

"Product Process and Laboratory Nonconformances."
"Supplier Nonconformances."
"CAPA System."
"Analytical Laboratory Investigation Procedure."

CAPA in the Pharmaceutical and Biotech Industries. http://dx.doi.org/10.1016/B978-1-907568-58-9.00013-8

4. Associated materials

N/A

5. Definitions

Correction: An action to eliminate/contain a detected nonconformity. Initial product disposition defines the recommend product correction for a product nonconformance.
Electronic system: Electronic application used to document event created as a result of a nonconformance.
Hold/quarantine location: Physically segregated and controlled area where nonconforming, rejected, expired, and obsolete material, as well as suspect nonconforming material currently under investigation, will be housed.
Material: A general term used to denote raw materials, starting materials, in-process materials, intermediates, packaging materials, and finished medical devices.
Nonconforming product: A material that fails on testing or inspection to meet defined specifications or has been manufactured using an unauthorized or deviating process.
Nonconformance report (NCR): Report used to document the specific nonconformance, specification, investigation, action required, and action taken to correct the nonconformance.

6. Responsibilities

Quality assurance (QA)

- Ensures that procedures are established for reporting and handling of nonconforming products and materials, including nonconforming samples obtained through customer complaint, clinical, or R&D activities.
- Ensures compliance of reworked or reprocessed materials with regulatory registration requirements and specifications. If required, QA confirms the necessary registration approvals with international regulatory affairs prior to rework or reprocessing and authorizing product disposition approvals.
- Possesses overall responsibility to oversee all nonconforming product investigation activities.
- Maintains the custody, and where necessary witnesses the disposal, of all identified and segregated nonconforming materials retained in the hold/quarantine location.
- Is responsible for product disposition decisions.

Operations

- Responsible for identifying, investigating evaluating, reporting, handling, and documenting nonconformities as well as taking appropriate CAPA.
- Responsible for the implementation of procedures for reporting and handling of nonconformities, including obtaining and documenting approval from QA for reworking or reprocessing operations.

Laboratory/quality control management

- Ensures that all test results generated are accurate and valid and ensures all lab/inspection personnel are aware of potential problems with testing.

Laboratory analyst/quality control (QC) inspector

- Awareness of potential problems of testing that could create nonconforming or OOS results and prompt reporting of these results when they occur.

Materials/warehouse department

- The coordination, execution, and documentation of physical material disposition in accordance with safety/HSE-compliant method.

Safety/health safety department

- Responsible for evaluating the way the material will be disposed when not covered by local procedural controls.

7. Requirements

7.1 Each operational unit must handle nonconforming product according to this procedure to ensure compliance with regulatory requirements and to guarantee full traceability of activities.

7.2 Any individual becoming aware of a material suspected to be nonconforming has the responsibility to report the incident to QA and originate a notification in the electronic system. The investigation and product disposition will be documented within this system.

7.3 Identification and segregation

7.3.1 QA defines hold activities and authorizes the quarantine of lots related to the nonconformity incidents. Nonconforming materials and/or products must be labeled or otherwise identified as to their nonconforming status and to subsequently prevent their use or sale. At a minimum, nonconforming product identification must contain the following information:

Product identifier (part or code number), lot number, and quantity. The entire scope of suspect nonconforming units must be identified. This may require manufacturing or distribution reconciliation activities as appropriate.

A statement that identifies the status of the material (i.e., quarantine).

The nonconformance notification (NCR) number or reference nonconformance source document (including validation protocols, experimental protocol number, etc.).

The date that the material or product is placed on quarantine.

7.3.2 Consideration must be given to the following scenarios to verify and ensure that all potentially nonconforming product is identified and properly controlled:

Product in transit to a distribution center from the manufacturing location, if applicable.

Product located at a distribution center that has been moved to the dock or already loaded for shipment.

Product that has already been returned to a distribution center and that may have been placed back into inventory awaiting shipment or into a damaged goods staging area.

Product that has already been distributed to the market.

7.3.3 In the instance of returned goods, the product must be inspected and documented that product meets specifications prior to release for redistribution. Should returned product be identified as not meeting specification, it will not be viable for release, and the product will be regarded as nonconforming.

7.3.4 Suspected nonconforming materials and/or products must be physically segregated and stored according to their status via placement on quarantine status away from acceptable materials and/or products in a timely manner.

The materials and/or products must be moved to a designated quarantine/hold area. The segregation of quarantine product must be documented in the electronic system, as a remedial action, as confirmation for the completion of this action.

Physical identification, segregation, and material status is not required where product inventory is controlled by a validated computer system that possesses identification and product status functionality.

7.3.5 For materials that require storage restrictions like flammable or refrigerated materials, they will be kept physically in their storage location (being segregated to the greatest extent possible), and they will be physically identified as potentially nonconforming.

7.3.6 If a temporary designated area is required, it must be constructed with the following required parameters:

Location is clearly identified as a hold/quarantine location with highly visible signage.

Location is physically segregated in proximity from released or in-process inventory.

Location is physically contained so as to prevent the commingling of affected product with released or in-process inventory. This may include temporary containment measures such as shrink wrapping, barrier tape, or roping.

Limited access will be strictly enforced to only authorized personnel.

Product within the location possesses appropriate site QA status identification form.

Noted in validated computer system that possesses identification and product status functionality, where applicable.

7.4 Evaluation and investigation

7.4.1 The evaluation of the nonconformance must include, but is not limited to the following:

A determination of the need for a more detailed investigation. If product or material nonconformity is confirmed, QA together with production will perform and document an initial investigation to assess the extent and the criticality of the failure with regard to compliance, efficacy, and safety and decide upon further steps to be taken.

The notification, as needed, of the persons responsible (including suppliers) for the nonconformance and immediate actions to be taken.

The entire scope of nonconformance evaluation and investigation requirements, which include identification of nonconformance scope, performance of RCA, identification and execution of CAPA can be found in **SOP 101**.

7.5 Initial and final disposition of nonconforming products

7.5.1 As a result of the nonconformance investigation, corrections will be proposed to remediate the effect, or potential effects, of the nonconformity. Initial disposition must be in accordance with the requirements below:

Quarantine: Product is segregated and controlled.

Return to vendor: Product is unacceptable, cannot be used, and will be returned to vendor. All vendor returns will be coordinated with purchasing and communicated to the applicable supplier representative. This must be documented and included in supplier quality metric review processes.

Sort: Product is inspected to defined requirements; acceptable product is separated from nonconforming. Where product is sorted, the product must be subject to subsequent inspection against current and approved product specifications.

Rework: Product is subject to additional processing steps outside the established manufacturing process. Any disposition for rework will require an approved and validated rework procedure that includes or references retesting and reevaluation of the nonconforming material/product after reworking.

- The rework procedure must be approved by the same functional groups that approved the current corresponding procedures. This is to ensure that the material/product meets its current approved specifications.
- Reworking and reevaluation activities, including a determination of any adverse effect via the existing or new risk analysis from the rework upon the material/product, must be documented and attached to the investigation nonconformance.

Reprocess: Subjecting a material that does not conform to standards or specifications to one or more processing steps by repeating chemical or manipulation steps that are part of the established manufacturing process, for example, resterilization and reinspection. Reprocessed materials must undergo retesting to current approved specifications prior to release.

Reinspected: Product is inspected again.

Use as is: Any disposition to use as is must include consideration of product acceptability and applicable regulatory requirements. The justification for use of nonconforming materials and/or products must be based on risk analyses that provide objective evidence displaying that its use will not adversely affect product form, fit, or function. The signatures of all individuals involved in the review and approval of product concessions must be documented on the investigation nonconformance. Any use as is determination must be reviewed and approved, at a minimum, by QA.

Other: To be selected when more than one disposition applies (i.e., multiple lots within the same nonconformance record and have different dispositions or when disposition given is not listed).

N/A: Not applicable.

7.5.2 As part of final QA review, QA will evaluate the proposed initial correction and will approve or revise the initial product disposition proposal. QA confirmation or revision of initial product disposition must be documented. Their evaluation will include assessment of the following (if applicable):

The initial scope of the nonconformity.

Compliance with regulations and standards.

Potential impact of proposed disposition decisions on product registration status.

R&D and design requirements.

The significance of the failure.

The detectability of the nonconformance.

The ability to rework/reprocess the device without adversely impacting product quality, safety, or efficacy.

This review may require additional support by further studies such as stress tests, etc.

7.5.3 The action of disposing/destroying nonconforming material/product must be conducted by appropriate internal personnel or approved contractors. Disposal and destruction of materials, products, and/or items will be conducted in accordance with local internal control procedures and must be recorded and verified by QA and documented on the NCR investigation nonconformance.

7.5.4 Upon completion of the authorized product corrections as defined within the nonconformance notification, QA will authorize a final product disposition.

7.5.5 When reworking, reprocessing, sorting, or partial scrapping of product is involved, the final product disposition will be based upon the results of reinspection to current approved specifications. Evidence must be provided. Final product disposition decisions and the corresponding QA approver of final product disposition will be documented within the nonconformance notification. Final product disposition options consist of the following:

Reject: Product is unacceptable and cannot be used. In this instance, the product will remain as nonconforming and will require subsequent disposal/destruction.

Accept: Product is acceptable and can be used. In this instance, product will be placed back in releasable inventory.

Other: To be used only in instance where multiple final dispositions are involved. In this instance, the accept/reject disposition in relation to the lots/quantities to which it applies must be documented.

N/A: Not applicable.

Scrap: Total or partial rejection of product or material.

7.5.6 Final product disposition (including product returns, destruction, or scrapping of materials) cannot be executed until all corrections relevant for the release of the material/product have been completed.

7.6 Documentation

7.6.1 All product nonconformances must be documented in the electronic nonconformance system.

7.6.2 Reference to the nonconformance notification number must be documented in all affected batch records.

Procedure example #2:
OOS: SOP

Table of contents

1. Purpose

This document describes the procedure for conducting investigations of OOS results in QC at ABC Company.

This procedure applies to in-process, drug substance, drug product, raw material, stability, cell bank, and validation sample results that are OOS, unless an investigation/retesting procedure is specified in the assay specific protocol or test method.

2. Scope

This document applies to investigation of results that do not meet the required specifications for in-process, OTC drug product, and stability and raw material samples.

This procedure does not apply to samples that do not meet alert, action, or control limits. It does not apply to environmental monitoring water samples.

This procedure does not apply to assays that are repeated due to an assay failure or a failure due to interference from components in the test sample (e.g., endotoxin testing). In these cases, the original assay or sample result is considered invalid, and the repeat analysis of the assay and/or sample replaces the initial result but is not considered a retest.

This procedure does not apply to aberrant data investigations or to samples without specifications.

3. Responsibility

- QC
  - Quality control analysts are responsible for notifying QC management when an initial OOS test result is obtained.
  - QC management or designee is responsible for notifying manufacturing, QA, and project management whenever an OOS test result is obtained.
  - QC is responsible for conducting OOS laboratory investigations.
- Manufacturing (or group that produced sample)
  - Manufacturing is responsible for conducting an investigation into a possible manufacturing or sampling issue that could cause the suspect result; QA will be consulted as necessary to complete investigations.
- Facilities and engineering
  - Facilities and engineering is responsible for confirmation of equipment performance, such as calibration status, PM status, and open work orders.
- QA
  - QA is responsible for reviewing and approving OOS laboratory and manufacturing investigations.
  - QA is responsible for approving any resampling and/or retesting.
  - QA is responsible for closing OOS reports, scanning the final reports to software system, and closing software system records.

- Contract laboratory (if applicable)
  - All contract laboratories used by ABC Company must have a defined OOS investigation procedure in accordance with published regulatory guidance on investigating OOS results or follow ABC company OOS procedures.
  - QC personnel will review laboratory investigations of OOS results for tests performed by contract laboratories and will address any issues in conjunction with ABC company's QA.
- Suggested timelines for completion of the investigation are as follows:
  - Same shift as discovery of OOS result: Review all preparations, instruments, and assay documentation for internal investigations (Phase I).
  - 14 days from discovery: Complete laboratory investigation (Phase II, if applicable).
  - 14 days from discovery: Complete manufacturing investigation.
  - 21 days from discovery: Decide to retest, investigate further, or report OOS.
  - 30 days from discovery: Retesting complete, if applicable, investigation closure, QA approval. If more time is required, QA may approve an extension.

4. Related documents

Laboratory investigation report for: Phase I
Laboratory investigation report form: Phase II
Manufacturing investigation
Investigation retest completion form

5. Safety

N/A

6. References

- Guidance for Industry: Investigating OOS Test Results for Pharmaceutical Production, FDA Draft, October 2006.

7. Definitions/Acronyms

Accelerated/stressed stability sample	Samples that are stored at unintended conditions to assess the effect on the drug substance or drug product. Such studies may include high/low temperatures; high/low humidity; photostability; freeze/thaw cycles; and/or other testing for a specific condition of concern on applicable products.
Assay failure	Failure of an assay to meet its specifications (i.e., standard curve, correlation coefficient, percent CV, control ranges, etc.) due to analyst, equipment, or reagent error.
CAPA	Corrective action/preventive action
CDER	US Department of Health and Human services, FDA, Center for Drug Evaluation and Research.
Initial OOS	Unconfirmed reportable result that is outside the acceptance criteria stated in the product or material specification.

OOS result	A result that fails to meet its final product specification.
Orthogonal testing	A method that uses a different methodology to evaluate the validity of an initial result. For example, one could evaluate whether an High-Performance liquid Chromatography (HPLC) sample was diluted improperly by testing the sample for total concentration by UV.
OOS	A confirmed reportable result that is outside the acceptance criteria stated in the product or material specification.
Qualitative test	A test where the result is descriptive, relative to the standard, or reported only as pass/fail. Numeric measurements may be generated for the attribute, but the test may be still considered qualitative (e.g., comparable to reference determined by percent difference of reference and sample characteristics).
Quantitative test	A test where the result is a measurement of a characteristic of the sample, reported as a numeric value.
Reject limit	An in-process product/process specification.
Repeat testing	Test performed on the same original sample after an original result has been invalidated. Repeat test results replace the initial result.
Reportable result	A final result reported as required by the test procedure. This reported result may be comprised of a single test measurement or, if required by the test method, may be the average of multiple test measurements.
Resample	Sample obtained after initial sampling event from the same source of the original sample (e.g., same process tank or bulk raw material container).
Retest	Additional testing performed on the original sample and/or resamples, when applicable, where no assignable cause for the original sample failure can be established.
Sample	An aliquot removed from the source to be tested, for example, directly from the process or bulk material.
Specification	A list of tests, references to test procedures, and acceptance criteria that are numerical limits, ranges, or other criteria for the tests described. Specifications establish the set of criteria to which the drug substance, drug product, cell bank, and raw material should conform to be considered acceptable for its intended use. Specifications are critical quality standards that are proposed and justified by the manufacturer/customer. Drug substance and drug product specifications are approved by regulatory authorities as conditions of approval.

8. Initial OOS identification and investigation initiation

Note: If possible, all dilutions, pipettes, intermediate reagents, intermediate sample preparations, sample vials, etc., should be saved for possible investigation for every assay until data has been reviewed and investigation work, if necessary, is complete.

8.1 Upon obtaining an initial OOS result, the analyst performing the assay should verify assay validity.

8.2 If any of the assay acceptance criteria/system suitability fail, invalidate the assay and perform a single repeat analysis.

8.2.1 Investigate possible causes for system suitability/assay failure and remedy the problem prior to repeating the assay.

8.2.2 This repeat assay result when performed on a valid assay will be considered the original result. The repeat assay is not a retest.

8.3 If all system suitability and assay acceptance criteria are acceptable, the analyst must immediately notify a QC supervisor or designee of the OOS.

8.3.1 Supervisory notification should be the same shift as the occurrence and confirmation of the OOS.

8.4 The supervisor or a designee experienced in the assay performed must review the assay to confirm the assay was performed and documented accurately.

8.5 If the assay or sample result is deemed invalid, the OOS result is not reported. The initial assay or sample result is invalidated. Proceed to Step 8.2.

8.6 If the assay and OOS result are determined to be valid, the OOS is confirmed.

8.7 Immediately upon confirmation of the OOS, QC initiates an investigation to record the OOS event. The number generated by software system will serve as the OOS number and is to be recorded on all associated OOS investigation forms and supplements.

8.7.1 In the short description field in the software system, enter detail that describes the report. The short description must include at least the following:

8.7.1.1 An indicator of the test sample type (including, but not limited to):

8.7.1.1.1 Stability for stability samples

8.7.1.1.2 Drug substance release

8.7.1.1.3 Drug product release

8.7.1.1.4 In-process for process intermediate samples

8.7.1.1.5 Raw material for raw material samples

8.7.1.2 The term *OOS*

8.7.1.3 The sample batch number

8.7.1.4 The sample part number

8.7.1.5 The test name (e.g., RP-HPLC or endotoxin)

8.7.1.6 The result that failed (e.g., purity or protein concentration) and the LIMS ID.

8.7.2 All other sections of the investigation report should be completed as applicable based on the assay data.

8.7.3 QC management must notify project management via email of the OOS result.

8.7.4 Project management must notify the applicable customer of the OOS event and ongoing investigation within 48 h of the confirmed OOS.

9. Laboratory investigation Phase I

9.1 The analyst who discovered the OOS and QC supervisor or designee must immediately perform Phase I of the laboratory investigation. Document investigation on laboratory investigation form. The analyst who ran the assay must complete Phase I and/or be interviewed by the supervisor or designee regarding performance of the assay the generated the OOS.

9.2 The stability specific section on investigation form and the conclusion of the investigation are to be completed by stability personnel if the sample is a stability sample, otherwise the stability specific section is N/A, and the conclusion is completed by laboratory personnel.

9.3 The following questions are intended to guide the investigation and ensure that a thorough investigation is performed. It is not intended to be inclusive of all possible variables that may be investigated. The investigation is not limited to only the questions listed below.

9.3.1 Review analyst performance of the method.
- Is analyst trained on current method?
- Was the correct revision of the method used?
- Did the analyst follow each step of the method correctly?

9.3.2 Inspection of assay data and calculations.
- Was the data interpreted correctly (e.g., integrations, baseline, and blank subtraction)?
- Was raw data and sample identification transcribed correctly for calculations?
- Were the calculations performed correctly?
- Were any applicable correction factors applied properly?

9.3.3 Inspection of the original sample:
- Did the sample appear as expected: color, clarity?
- Was the timing of the sample delivery as expected?
- Was the sample container intact and free from damage?
- Was sample stored at correct storage condition?

9.3.4 Sample preparation:
- Were the dilutions prepared properly and accurately?
- Was the correct diluent used?
- If applicable, was the protein concentration correct and reviewed?
- Were correct weights, volumes, and materials used (e.g., volumetric pipettes, flasks, filters, etc.)?

9.3.5 Inspection of instrumentation:
- Was the instrument(s) within its calibration interval?
- Was the instrument(s) functioning normally (e.g., typical response, pressure, leaks, clot times, resolution, tailing)?
- Were the instrument parameters and sequence steps correct?
- Were samples and standards analyzed in the correct order?
- Did other samples tested on the same sequence produce expected results?

9.3.6 Inspection of reagents, controls, and reference standards:
- Were the reagents prepared correctly and within use-by-date?
- Was the glassware used visibly clean and lacking defects?
- Were the controls, reference standards, and standard curves prepared correctly?
- Was sample within use-by-date, if applicable?
- Reference standard and control results are acceptable or within expected range?

9.3.7 If the OOS is for a stability sample, proceed to Step 9.3.8 to complete stability questions; if not, then N/A stability section.

9.3.8 Stability
- Is this an accelerated or stressed condition for stability?
- Is this a bag study?
- If it is a bag study, how much weight did it lose?
- Are other lots on stability having testing at this time point and condition?
- If other lots are on stability and have been tested at the same time point and condition, were results OOS at this time point and condition?

9.3.9 Any answers to the above questions that could impact method or sample validity must be further discussed in the comments section on the inspection form.

9.3.10 Once checklist and Phase I investigation is complete, analyst and QC supervisor/designee will review and sign. Ensure that the software system record number is clearly visible on every page of the report.

9.3.11 Determine if the laboratory investigation Phase I identified an assignable cause or that the assay or sample result is invalid.

> Note: If an accelerated or stressed stability sample is OOS and the assay is determined to be valid, no further investigation will be performed; the investigation may be closed at Phase I and the sample dispositioned.

9.3.11.1 If the assay or sample analysis is determined to be invalid during Phase I investigation, a repeat assay may be appropriate. Contact QC management or designee to approve prior to invalidating the initial assay or result and repeating the analysis.

9.3.11.2 If there is an assignable cause, verify and/or explain how the cause identified would result in the observed OOS result.

9.3.11.2.1 Obtain signatures from QC management and QA to approve explanation prior to dispositioning the sample and closure of the investigation at Phase I.

9.3.12 If there is no assignable cause or determination that the assay is invalid, notify QA, manufacturing, and the project manager and proceed to Phase II.

9.3.12.1 Obtain signatures from QC management and QA to close Phase I before proceeding to Phase II. Ensure that the software system PR number is clearly visible on every page of the report.

9.3.13 The operations investigation, if applicable, and laboratory investigation Phase II are performed in parallel.

9.3.14 Once Phase I investigation has been signed by QC and QA, QA scans a copy and attaches it to the PR report in the software system along with any other supporting documentation. Via software system notification, QA sends notice to QC management that Phase I is complete.

9.3.15 In the event the investigation must go to Phase II and/or manufacturing, QC must initiate Phase II, and they must also notify manufacturing management that the operations investigation is needed; this should be done through the software system so that all information regarding the OOS sample is readily available.

9.3.16 QC documents Phase II laboratory investigation on form number?

9.3.17 Manufacturing documents the manufacturing investigation on form number?

10. Laboratory investigation Phase II

10.1 The following questions and investigation guidance are intended to guide the investigation and ensure that a thorough investigation is performed. It is not intended to be inclusive of all possible variables that may be investigated. The investigation is not limited to only the questions listed below. Document Phase II investigation details using an investigation form and include supplemental documentation as necessary (this includes, but is not limited to, memoranda, reference documents, other reports, etc.).

10.2 The specific details of the investigation should be captured in a summary memo attached to the relevant investigation.

10.3 Review control charts associated with the assay for other out-of-control points or trends:

10.3.1 Do the control charts of the assay controls and sample results indicate a trend?

10.3.2 Do different reagent lots result in significantly different sample or control results?

10.3.3 Is there significant difference between analysts in regard to control and sample results?

10.3.4 Are there any other differences that might be the cause, e.g., different instruments, columns, or detectors?

10.4 Review of other test results for trends:

10.4.1 Do other tests performed on the suspect sample, step, or prior step yield suspect results?

10.4.2 If so, do those results or parameters correlate with the OOS result?

10.5 Investigate sample/interassay control/reference standard/sample preparations through appropriate informational testing.

> Note: Original sample cannot be reanalyzed at this point. Keep original sample at appropriate storage condition.

10.5.1 Can the sample be tested with orthogonal methods either internally or by outside testing houses?

10.5.1.1 Do the orthogonal test results support or refute the suspect result?

10.5.2 Are there intermediary dilutions of the suspect sample?

10.5.2.1 Analyze the dilutions or preparations that may identify a possible sample preparation or instrument error in initial testing.

10.5.2.2 Proceed with preparation from an intermediary step prior to the final assay step and analyze for information only. This analysis cannot replace the original result.

10.5.2.3 Reanalyze the new preparation from the intermediary step of the suspect sample. For example, reinject an HPLC auto-sampler vial. This analysis cannot replace the original result.

10.5.2.4 Is the suspect result repeatable with the same preparation?

10.5.3 Is there any further informational testing that can be done?

10.6 Investigate instrument performance.

10.6.1 Are there any calibration check results that might correlate with the suspect value?

10.6.2 Are the pipettes used in the assay delivering correct volumes?

10.7 Determine if the laboratory investigation Phase II identified an assignable cause or that the assay or sample result is invalid.

10.7.1 If the assay or sample analysis is determined to be invalid during the Phase II investigation, a repeat assay may be appropriate.

10.7.2 If there is an assignable cause, verify and/or explain how the cause identified would result in the observed OOS result.

10.7.3 Notify QA and manufacturing investigators, if applicable, if an assignable cause, an invalid sample, or an invalid assay was identified so further manufacturing investigation may stop.

10.7.4 Contact QC management and QA to approve explanation prior to performing a repeat analysis and/or to close the investigation at Phase II.

10.8 Obtain signatures from QC management and QA to close Phase II. Ensure that the software system PR number is clearly visible on every page of the report, including the investigation form and all supplemental information. On approval, QA scans a copy of the completed investigation to the PR report and notifies QC management via the software system that Phase II has been completed.

11. Manufacturing investigation

11.1 Manufacturing must conduct operator interviews and process review of all relevant manufacturing and sampling steps.

11.2 Manufacturing and/or QA must perform an expedited review of all relevant batch record data and provide any information to aid in the OOS investigation.

11.3 Manufacturing must document the manufacturing investigation document using investigation form. Include supplemental documentation as necessary including, but not limited to, memoranda, reference documents, and other reports.

11.4 Determine if the manufacturing investigation identified an assignable cause for the OOS result.

- 11.4.1 Retesting is not required or allowed if a determinate manufacturing error is identified or data from other manufacturing steps confirms the OOS.
- 11.4.2 If there is an assignable cause, verify and/or explain how the cause identified would result in the observed OOS.
- 11.4.3 Notify QC investigators if an assignable cause was identified and to stop further investigation.
- 11.4.4 Contact QC management and QA to approve prior to invalidating the initial sample analysis and to close the investigation at the manufacturing investigation stage.

11.5 Once the manufacturing and QC Phase II investigations have been signed by area management and QA, QA scans a copy and attaches it to the PR report in the software system. Ensure the software system PR number is clearly visible on all pages of and any supplemental information attached. Via software system notification or email, QA sends notice to QC management and manufacturing management that the OOS investigation is completed and informs if retesting is authorized or not.

12. Disposition/retest determination

12.1 If a determinant cause for the suspect result is not discovered, contact representatives from the following areas, as applicable. These individuals will evaluate laboratory and manufacturing investigations and propose the path forward:

- 12.2.1 Manufacturing supervisor and/or designee for the submitting suite
- 12.2.2 Vendor technical service representative (for raw material investigations only)
- 12.2.3 QA
- 12.2.4 QC manager or designee

12.2 No retesting may be performed without performing an OOS investigation, documenting the rationale for the need to perform a retest to determine the true value of a sample, and documenting the retesting plan.

12.3 If at the completion of the laboratory and manufacturing investigations an assignable cause for the suspect result is not identified, all investigation data is presented to the investigation team to assess the information and make a recommendation to investigate other options, fail the sample, or perform a retest of the sample.

12.4 Retesting must be based on scientifically justified rationale, where the initial result may not be representative of the true value of the sample and a retest is required to determine the true sample value.

12.5 Retesting will be performed in accordance with retesting procedures described in this document.

12.6 QC management and QA must approve the preliminary OOS investigation, the rationale to retest, and the retest plan prior to performing retesting. QA and QC must also approve if the decision is to fail/disposition the sample without retesting.

12.7 Retesting is documented on form. QC completes the retest information and submits to QA for approval. QA approves the retest completion form and attaches it to the software system record.

13. Resampling

13.1 If the integrity of a sample or container is suspected that it may have been compromised (e.g., cracked, contaminated, thawed inappropriately) or the cause of the suspect/invalid result may be due to a sampling error, then a new sample from the same point in the process or from a different container of the same lot/batch should be obtained for repeat analysis or retesting.

13.2 The rationale for resampling must be documented and approved by QC management and QA prior to resampling.

13.2.1 Customer may sign in agreement of this resampling decision if applicable.

13.3 If a new sample cannot be obtained, contact QC management for further course of action. The further course of action will be described in a memo approved by both QA and QC management.

14. Retest procedure

14.1 Where possible, a different analyst than the analyst who generated the suspect OOS result and who is at least as experienced should perform the retest. If possible, the retest should be performed on separate occasions to incorporate any potential assay variability.

14.2 Retesting must be performed using the original sample or another sample (container) sampled at the same time from the same process step.

14.3 For qualitative assays perform three (3) additional, separate analyses, and proceed to Section 14.4. Each test result must be evaluated before proceeding to the next test.

14.3.1 Raw material bioburden assays are considered to be qualitative assays.

14.3.2 Due to the definitive nature of qualitative test results (i.e., the sample either passes or fails), three retests is sufficient to determine the true value of the sample and exclude the possibility of a random, nonrepresentative result.

14.4. For quantitative assays, perform seven additional retest.

14.4.1 Any exception to this requirement must be approved by QA prior to performing any retesting.

14.4.2 Seven retests are to be performed to ensure that the true value of the sample is reported for quantitative testing.

14.4.3 If instrument performance is not suspected, all retests may be performed on the same run.

14.4.4 Sample preparations should be performed independently for each of the retests.

15. Disposition

15.1 Qualitative assay

15.1.1 If any retest fails, then the OOS result is confirmed and no further retesting is allowed. The reported result is the OOS result, and the conclusion of the OOS investigation is that the sample fails the specification.

15.1.2 If all of the retests meet the specification, then the OOS is not confirmed.

15.1.3 The original, suspect result must be considered when determining disposition of the sample, unless there is an assignable cause.

15.1.4 Disposition is based on original analysis, retest analyses, and the investigation.

15.2 Quantitative assay

15.2.1 If any retest result does not meet the specification and there is no explanation/root cause for the failure, the initial OOS result is confirmed and no further retesting is allowed. The reported result is the initial OOS result. The conclusion of the OOS investigation is that the sample fails the specification.

15.2.2 If any of the retest failures can be explained or there is a root cause for the retest failure, the investigation should continue as necessary. Disposition of the sample is based on the documented investigation and all results, including each applicable, individual retest result, and the initial OOS result.

15.2.3 If all retest results meet specification, all retest results, the OOS result, and the investigation will be used to determine disposition and the reported result.

15.2.4 The investigation and statistical analysis, if appropriate, will be used to determine whether the OOS result is considered representative of the sample or if it is an outlier.

15.2.5 If investigation yields a plausible explanation for the suspect result, then the suspect result may be considered nonrepresentative of the sample and may be excluded from the retest values and determination of disposition. All of the remaining retest values are reported.

15.2.6 If a single value is required for reporting purposes (e.g., LIMS, variable in other calculations, or CoA), the mean may be reported. However, disposition is based on all values, and the reported average must be linked to each individual retest result and the investigation (e.g., OOS report number should be recorded on batch record with all results recorded).

15.3 In the case of a confirmed OOS result, evaluate the potential impact on previous batches of the same material or reported results of the same sample.

15.4 Include corrective and/or preventive action in the investigation report or in another quality system.

15.5 Reference the OOS software system PR number on each associated assay form/packet.

15.6 QA and QC must approve final disposition and the investigation report.

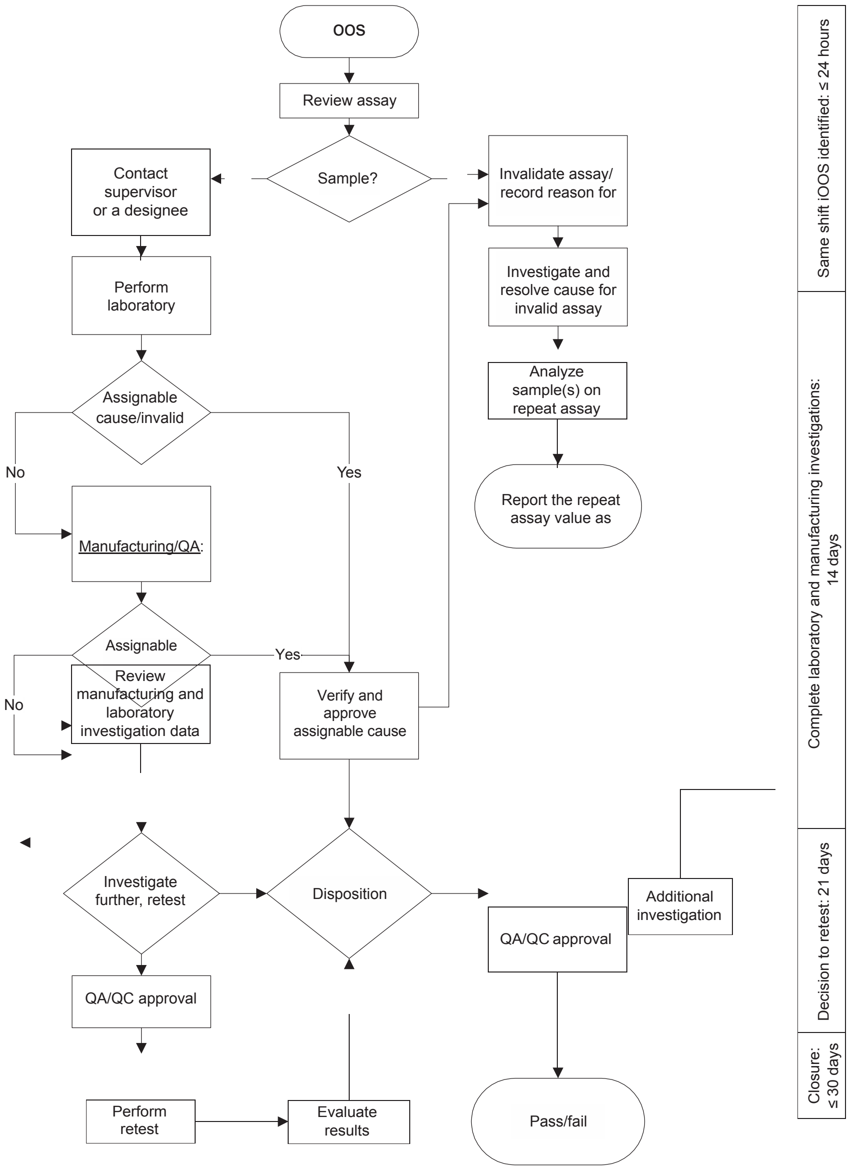
15.7 The completed OOS report is scanned by QA and attached to the software system PR and is filed in QA documentation. QA closes the software system PR.

15.8 Applicable CAPA determined by the investigation should be documented and tracked by the quality systems CAPA procedure.

16. Attachments

Attachment A: OOS investigation flow chart.

Attachment A – OOS investigation flow chart



Records

Records created as a result of this procedure will be maintained as described in the ABC Corp. Record Retention policy.

Procedure example #3:
SOP: corrective and preventive

1. Purpose

The purpose of this procedure is to define requirements for carrying out CAPA to avoid potential problems before they arise, as well as to prevent recurrence of nonconformances.

2. Scope

All CAPA generated from nonconformance investigations must comply with the requirements as defined by the procedure.

3. Training

All personnel responsible for documenting, managing, reviewing trending, and approving corrective or preventive actions will be trained on this procedure.

4. Specification

N/A

5. Frequency

N/A

6. Responsibilities

Global executive management

- Provide the global resources and emphasis necessary to prioritize and address global CAPAs in a timely manner and to ensure the health of the global CAPA process.
- Ensure that practices are conducted in compliance with this procedure.
- Ultimately responsible for ensuring the robust and compliant completion of CAPAs as warranted.

Global quality organization

- Establish a global CAPA administrator.
- Establish a program for global CAPA metrics, system monitoring, and reporting.
- Represent the global CAPA process at ABC Corp. management reviews.
- Represent those issues requiring major resources and capital to CV executive management.

- Support the CAPA process as subject matter experts.
- Review, assign, and approve all global CAPAs; it is the responsibility of the approver to verify all supportive information submitted with a CAPA.
- Ensure the dissemination of CAPA knowledge through global metrics, global CAPAs, and global quality council communications.

Global quality systems and reporting manager

- Manage global quality system data.
- Generate, monitor, track input source metrics, and escalate as needed.
- Review and define any unacceptable trends across sites and platforms.
- Evaluate nonconformances for possible CAPA inclusion based upon input source metric results as required.

Site operation management

- Provide the site resources and emphasis necessary to prioritize and address site CAPAs in a timely manner and to ensure the health of the site CAPA process.
- Ensure that practices are conducted in compliance with this procedure.
- Ultimately responsible for ensuring the robust and compliant completion of CAPAs as warranted.

Site quality council/leader

- Manage a site quality council (leader).
- Generate, monitor, and track all input source metrics.
- Review and define any unacceptable trends within site and processes.
- Evaluate nonconformances for possible CAPA inclusion based upon input source metric results as required.

Site quality management

- Consisting at a minimum of site general manager and quality head or equivalent quality unit.
- Provide the site resources and emphasis necessary to prioritize and address site CAPAs in a timely manner and to ensure the health of the site CAPA process.
- Establish a site quality council.
- Establish a program for site CAPA metrics and reporting.
- Review and approve CAPA records including the appropriateness of the proposed completion date, extension of due dates, transfer of ownership, change in scope, cancellation with proper justification, effectiveness check results (as applicable), and closure.

Initiator (based upon origination of nonconformance)

- Generate complete accurate and robust nonconformance notifications.
- Provide objective evidence to substantiate existence of nonconformance.
- Provide additional evidence/information for CAPAs as required.
- Participate in the investigation as a member of the investigation team.

Investigation chairperson/investigation team

- Develop and document the required CAPA plans and methods for determining effectiveness.
- Evaluate project and resource requirements, requesting any additional resources and capital required to successfully complete the CAPA plan and effectiveness measures.
- Generate necessary CAPA records and inform employees, functions, and department affected by the action.
- The investigation chair is ultimately responsible for the completeness of effective and robust corrective actions.

Effectiveness chair (based upon origination of CAPA and stage of CAPA)

- Evaluate effectiveness in accordance with the approved effectiveness criteria.
- Complete summary reports that define the level of success for effectiveness metrics.

CAPA administrator

- Responsible for the overall administration of the CAPA system.
- Assists in the development of system metrics.
- Manages and reports those metrics to global quality council leader and others as required.

7. Discussion

N/A

8. Definitions

Amendment: Additions, deletions, or changes to a fully approved nonconformance.
Assignable cause/root cause: The fully documented and scientifically justified source of the failure and explanation for the nonconformance/OOS results.
Correction: An immediate action to eliminate/contain a detected nonconformity. Whenever there is a potential nonconformance, correction should be implemented; however, a correction can be made without initiating a CAPA.
Corrective Action: (Also known as CAPA.) An action to eliminate the cause of an existing nonconformance or defect to prevent reoccurrence. The process includes defining the problem, finding the cause of the problem, developing an action plan to correct the problem and prevent its reoccurrence, implementing the plan, and evaluating the effectiveness of the corrective action.
Effectiveness check: A systematic and documented process that establishes whether an investigation and implemented CAPA plan were successful in eliminating the root cause and possibility of recurrence by the same cause.
Input Systems: Input sources are typically the various processes that measure the conformance or nonconformance of product, process, or system quality requirements.
Investigation: This nonconformance type is characterized by an event in which an investigation is required to determine the root cause and to identify corrective or preventive actions, if appropriate. An investigative nonconformance is required in any case where an evaluation of the potential impact to form, fit, or function is required. Consideration for potential impact to product stability as well as validation status should also be considered in this evaluation.

Nonconformance: A departure from an approved instruction, established standard, or an unexpected observation that could affect cGxP compliance or product form, fit, or function.
Preventive action: An action taken to detect and eliminate the causes of a potential nonconformance, nonconformity, or defect to prevent occurrence. Preventive actions are actions to reduce the probability that a potential problem will occur. The process includes identifying the potential problem or nonconformance, finding the cause of the potential problem, developing a plan to prevent occurrence, implementing a plan, and reviewing actions taken and their effectiveness in preventing the problem by the same cause.
Trend: A general direction in which data implies a process is moving.

9. References

Quality Policy #-001, Corrective and Preventive Action System.
SOP: CAPA and Nonconformance System.

10. Associated material

Form #, Due Date Extension request form.

11. Procedure

11.1 Corrective and preventive actions can be initiated not only to eliminate root causes associated with significant single incidents, unfavorable trends revealed through CAPA source data and reporting as well as initiate activities regarding opportunities for improvement (preventive action). A complete and robust investigation or, in the case of preventive action, a thorough situation assessment is a necessary prerequisite to determining the need and extent of action required. See **SOP # -001** for details regarding the necessary elements for nonconformance investigations.

11.2 A complete CAPA consists of the following elements:
- CAPA plan development
- QA approval and product disposition, where product was involved
- Execution of the CAPA plan and verification of actions
- Effectiveness check assessment
- Final approval

11.3 CAPA plan development

11.3.1 This CAPA plan must include the following:

For each root cause from the investigation, describe and justify appropriate corrective actions and/or preventive actions as applicable to correct and/or prevent reoccurrence or occurrence of the same deviation in the event being addressed and in other susceptible situations and processes.

Preventive action initiation follows the same path as CAPAs. An investigation outlining the situation and potential risks must be documented.

Clearly link each action to its root cause, where applicable.

The modifications to processes, procedures, or systems needed to correct and prevent the identified nonconformance. Documents that require modification should be listed specifically, and the changes should be described in general terms.

Any changes in a process, procedure, or in a system must be described in enough detail so that it is clearly understood what is to be done. The expected outcome of these tasks should also be explained.

Where processes/methods or applications are modified, corresponding validation tasks must be included in the CAPA tasks to ensure that the modifications do not adversely affect the device.

Documented and executed training activities where there are changes to processes or functions must be included.

Monitors or controls necessary to detect problem recurrence.

11.3.2 Each CAPA task in the CAPA plan must possess a corresponding due date and responsible person. Risk to processes and product(s), along with allowing a reasonable amount of time to complete the action, must be considered when determining the due date.

11.3.3 Identifying and ensuring touch points with upstream and downstream processes and procedures remain intact is vitally important. Consideration regarding processes and materials impacting product must be risk assessed and documented.

11.3.4 Previously assigned CAPAs may be utilized for future follow-up if QA agrees that the assignment of the existing CAPA is appropriate to the new incident. In this case, a new CAPA record does not need to be created, and the predicate CAPA number is cross-referenced in the notification.

11.3.5 The investigation team will also define the necessary effectiveness check criteria and time frame to ensure that the proposed CAPA plan is effective in eliminating or preventing the root cause. The effectiveness assessment must be clear, measurable, and objective.

11.3.6 Examples of effectiveness measures include but are not limited to the following:

Review of 3 months of ABC product release using a new process. No NCRs issued due to XYZ process problems.

Review 30 lots of XYZ material to determine if ABC measurement remains within 2 SD of the identified specification and is normally distributed, i.e., no trends, shifts in data over that time period.

Review of complaints from the last 6 months regarding ABC product, where there are no complaints logged regarding rough edges worldwide.

11.3.7 The time frame assigned to the effectiveness check must be established on a case-by-case basis. This time period must be correlated with the frequency of the process under evaluation.

11.4 QA approval

11.4.1 QA must agree to the due dates to ensure a timely completion of the actions. They will also confirm the adequacy and objectiveness of the proposed effectiveness assessment. QA will assign a person to be the effectiveness chair.

11.4.2 If the completed CAPA plan and effectiveness assessment are appropriate, QA, the associated operational manager, and any optional approvers (as needed) will approve the record.

11.4.3 If either the CAPA plan or effectiveness assessments are incomplete, inadequate, inaccurate, or erroneous, QA must reject the investigation, and it will be returned to the investigation chair for correction/completion.

11.4.4 QA will identify an effectiveness assessment chairperson.

11.4.5 Once the CAPA plans have been approved, the CAPA plan may be executed.

11.5 Execution of the CAPA plan

11.5.1 The responsible person for each of the CAPA action must complete their assigned task by the due date assigned. Objective evidence of the completion of each CAPA task must be attached to the CAPA record.

11.5.2 Example of objective evidence includes but is not limited to the following:
Training records
Validation reports
Change requests
Approved procedures with change history attached
Raw data with attached analyses
Reference any attachments that document the completion of the short term corrective actions to its root cause.

11.5.3 The individual assigned as the investigation chair is responsible for summarizing a complete listing of the actions that were taken to correct or prevent the problem, including a listing of all documents that were modified as part of the CAPA plan execution.

11.5.4 When the CAPA plan has been completed in its entirety, all CAPA tasks must be verified as complete by the investigation chair.

11.5.5 The investigation chair must also verify that the necessary, predetermined evidence for task completion has been provided, including completed status updates and extension requests.

11.5.6 They also verify where the training assessment indicates that training is required that the necessary training has been performed.

11.5.7 CAPA verification must be performed by an independent party from the individual having completed the task.
The CAPA is considered closed after all actions are completed, verified, and QA approves the record.

11.6 Effectiveness check assessment

11.6.1 The effectiveness assessment chairperson is responsible for executing the effectiveness assessment in accordance with the approved effectiveness check plan.

11.6.2 They must ensure that the objective evidence satisfies the CAPA effectiveness acceptance criteria, demonstrating that the executed CAPA plan was effective in resolving the root cause of the nonconformance or will indeed prevent occurrence of the potential nonconformance.

11.6.3 Examples of objective evidence include but are not limited to the following:
Raw and summary data of statistically relevant, related customer complaints on the specified product demonstrating no incidents in the field.
Raw and summary statistically relevant OOS or NCR data indicating no issues with the materials.
Raw and summary statistically relevant data of a batch record review indicating no issues with the production, testing, or release of the materials.

11.6.4 Objective results of the effectiveness assessment must be attached to the effectiveness check record to substantiate CAPA effectiveness. If the effectiveness assessment fails, this must be documented in the effectiveness check summary for subsequent QA rejection.

11.6.5 Upon completion of successful effectiveness check assessments, the record will be forwarded to QA for final approval.

11.7 Final approval

11.7.1 As part of approval, it is the responsibility of **all** parties to ensure that the following criteria have been met:
Were all of the objectives of the CAPA plan met?
Have all of the changes been completed and verified?
Have appropriate communications (through change control) and necessary training been implemented?

Has it been demonstrated that the executed corrective action plan does not have any adverse effects on the product or ancillary processes?

11.7.2 If the effectiveness assessment has been successful and the above criteria has been met, QA will approve the record, and all associated records will be closed.

11.7.3 If the effectiveness assessment proves that the implemented CAPA has been ineffective in resolving the root cause, QA will open a new investigation record or reopen the existing investigation, and they will identify a new investigation chair.

11.8 CAPA due date extensions

11.8.1 If the CAPA will not be approved before its due date, then a due date extension request **Form #ABC-001** must be submitted by the person responsible and reviewed and approved by the appropriate department supervisor.

11.8.2 By approving the extension request form, the department supervisor acknowledges scope, responsibility, and justification for extension. The department supervisor approves the proposed extension date.

Acceptable extension example: Based on the actions completed to date and the requirement to receive building occupancy permits from the county prior to completing the facility validation, additional time is required to complete Action #5. All other steps are completed.

Unacceptable extension example: Additional time is required. Actions #1–5 are not completed (no additional data provided).

11.8.3 After approval from department supervisor, the first extension request form is routed to QA manager or QA head for approval and attached to the corresponding electronic record.

11.8.4 By approving an extension request form, QA acknowledges that the scope and product impact have been identified and isolated. The proposed due date may be revised or approved by QA when adequate justification supports an extension.

11.8.5 A limit of two due date extension requests will be allowed for each individual record. If a second extension request is generated, then this must be approved by the department supervisor, site QA manager, or QA head and the general manager.

11.8.6 Extensions will be tracked, trended, and reported at quality council meetings.

11.9 Amendment of a closed CAPA

11.9.1 If additional information arises post-closure of a notification that will result in a change of the final disposition, QA authorizes and reopens the record and routes the record back to the investigation state.

11.9.2 Sufficient information must be provided in writing to QA to make an informed decision regarding the proposed amendment.

11.10 Changes to CAPA activities

11.10.1 At any point during the process, an update to the status of the report may be submitted by the investigation chair using the electronic system. QA disposition of request is required.

11.10.2 If the scope of the CAPA has changed, or an unforeseen event has occurred that will extend the activities beyond the original due date (e.g., a part for a piece of equipment scheduled to be delivered in 1 month was delayed for 3 months, or a preventive action is tied to the production schedule and the production schedule changes), an extension of the due date for the CAPA must be requested.

11.10.3 Any significant change in scope must be documented in the record in a timely manner.

11.10.4 If any change to a CAPA is reviewed and subsequently rejected by QA, then the reason for rejection and path forward must be documented in the nonconformance record.

11.11 Source data review and reporting

11.11.1 In an effort to identify and evaluate systemic issues for potential CAPA inclusion, routine metrics will be generated and reviewed as part of site quality council meetings.

11.11.2 At each ABC Corp. site, a quality council must be established or integrated into an existing data-driven team.

11.11.3 The site quality council will consist of, at a minimum, site QA head, site operations, quality system, and quality management.

11.11.4 On a monthly basis, site quality is responsible for developing and reporting metrics on all of their site's nonconformance occurrences via the quality council. These metrics must include, at a minimum the following:

Percent on-time closure of investigations and CAPA

Investigations and CAPA aging reports

Percent on-time closure and aging of records associated to internal audit observations (i.e., Novartis audits [GCA])

Percent on-time closure and aging of records associated to external audit observations (i.e., FDA, BSi, Health Canada)

Results of the analyses of these metrics must be documented.

11.11.5 On a quarterly basis, site quality will be responsible for rolling these metrics up into the site quality management review in accordance with **Quality Policy #-001**, quality management. In addition to the metrics described above, the following metrics must be collected and reviewed and the evaluation documented.

Pareto of nonconformances by root cause and product.

11.11.6 Appropriate statistical techniques must be employed in the development and analysis of these metrics. Any unfavorable trends or unexplained outlier occurrences will require documented consideration for the initiation of an investigation nonconformance.

11.11.7 It is the responsibility of the quality council leader to initiate an investigation based upon input source data analysis and to substantiate the decision not to initiate investigation.

11.11.8 The results of CAPAs must be appropriately disseminated to parties directly responsible for assuring the quality of product and prevention of quality problems. Meeting minutes, metrics, and any initiated investigation details coming out of site quality council meetings will be distributed to all affected organizational departments.

11.11.9 Nonconformance and CAPA metrics will be submitted to ABC Corp. global management review.

12. Results

N/A

13. Records

N/A

Procedure example #4:
SOP: FMEA SOP

1. Purpose

1.1 The purpose of this procedure is to provide a systematic approach for recognizing potential failure modes and analyzing their effects on product design and manufacturing processes. This procedure is intended for identification and elimination of potential failure modes or to continuously minimize the effects of those failures that cannot be avoided. The procedure will also provide follow-up CAPA to ensure that the chance of a potential failure could be eliminated or reduced.

2. Scope

2.1 This procedure establishes requirements and tools for performing a failure mode, effects, and criticality analysis on development products and processes. Each potential failure is ranked by the severity of its effect so that appropriate preventive/corrective actions may be taken to eliminate or control the high risk items.

3. References

3.1 Quality System Regulation 21 CFR 820.30 (g).
3.2 MIL-STD-1629A: Military Standard Procedures for Performing a Failure Mode, Effects and Criticality Analysis.
3.3 MIL-STD-882C: Military Standard System Safety Program Requirements.
3.4 ISO 14971-1 Medical Devices—Risk Management Part 1: Application of Risk Analysis to Medical Devices.
3.5 FDA Guidance.

4. Definitions

4.1 **Failure modes, effects, and criticality analysis (FMECA)**: A procedure by which each potential failure in a system is analyzed to determine the results or effects thereof on the system and to classify each potential failure according to its severity.
4.2 **Failure mode**: Describes the way in which a product or process could fail to perform its desired function.
4.3 **Process effect**: All the effects of each failure mode including current step effects and downstream subassembly effects.
4.4 **End effect**: An adverse consequence that a failure mode has on the function of the device.
4.5 **Design FMECA**: To analyze the potential failure modes of the product design.
4.6 **Process FMECA**: To analyze the potential failure modes of the manufacturing processes that build the product.
4.7 **Occurrence**: Estimate how often this failure is expected to occur. Only controls intended to prevent the cause of failure from occurring should be considered in this estimate.

4.8 **Severity**: Estimate how severe the effect of this failure is on the end user. Severity is the factor that represents the seriousness of the failure to the customer after it has occurred.

4.9 **Detection**: Can the problem be detected prior to distribution or by the customer before damage occurs?

4.10 **Risk priority number (RPN)**: It is a mathematical product of the numerical severity, occurrence, and detection ratings (RPN = (S) × (O) × (D)).

5. Responsibilities

5.1 Design FMECA team—The team may consist of, but is not limited to, the following personnel:

5.1.1 Process development engineer
5.1.2 Clinical specialist (optional)
5.1.3 QA
5.1.4 Manufacturing engineer (optional)
5.1.5 Marketing representative (optional)
5.1.6 Technical services (optional)

5.2 Process FMECA team—The team may consist of but is not limited to the following personnel:

5.2.1 Manufacturing engineer
5.2.2 QA
5.2.3 Production
5.2.4 Technical services (optional)
5.2.5 Process development engineer (optional)

6. Procedure

6.1 During product and process development, the team should meet for the sole purpose of creating and defining the FMECA.

6.2 The first step of the FMECA is to provide a description of the item to be analyzed and a concise definition of its functions.

6.3 The next step is to identify potential failure modes. A review of past FMEAs, quality, and a complaint history on comparable components is a recommended starting point.

6.4 For each potential failure mode identified, a concise description of the effects of the failure should be developed. Assume the failure has occurred and describe what the customer might notice or experience.

6.5 List all potential causes assignable to each failure mode. A failure mode can have more than one cause, and all possible independent causes for each failure mode must be identified and described.

6.6 The controls that currently exist to prevent the cause(s) of failure from occurring or are intended to detect the cause(s) of failure should be listed and assigned a numerical rating from 1 to 5 based on occurrence, severity, and detection. The numerical ratings for occurrence, severity, and detection are listed in Attachment #1 for design FMECA and Attachment #2 for the process FMECA.

6.7 The three numbers are multiplied times one another resulting in a RPN from 1 to 125 as shown in Table 6.7. Failure modes will be sorted by RPN in ascending order. The RPN provides a

Table 6.7 **Risk priority index**

Risk priority index	Risk and functionality level	Action
1–30	High risk	Risk is unacceptable and must be reduced.
31–60	Moderate risk	Risk is marginally acceptable and should be reduced as low as reasonably practicable; technical and economic practicalities are balanced against risks/benefits.
61–125	Low risk	Risk is acceptable, and risk reduction can be considered if feasible.

relative indicator of all the causes of failure. The highest RPNs and occurrence ratings should be given first priority for corrective actions. As a tool for risk prioritization and change analysis, the following scale was formulated:

6.7.1 To reduce the probability of *occurrence*, process or design revisions are required.

6.7.2 To reduce the *severity* of product failure modes, design/process actions are required.

6.7.3 To increase the probability of *detection*, process changes may be required.

6.8 When the highest severity level (5) is applicable, this failure will be considered as *high risk* and should be reduced by revising the design/process or by introducing positive detection of the cause of failure. If the severity level (5) cannot be reduced, a documented justification will be required that explains the reason for why this high risk is acceptable.

6.9 Document all actions taken to reduce the RPN, and reference all documents, test reports, statistical analyses, etc., that verify the preventive/corrective action. Calculate new RPNs, and determine future courses of action.

6.9.1 The FMECA process will be performed a minimum of two times. The first FMECA will analyze the failure modes, effects, and risk priority. The second FMECA will concentrate on the preventive/corrective actions and risk reduction.

6.10 Based on the FMECA analysis, design and/or process actions can be used for the following:

6.10.1 Eliminate the cause of failure.

6.10.2 Reduce the probability of occurrence by reducing the probability that the cause of failure will result in the failure mode.

6.10.3 Reduce the severity of failure by redesign to produce a fail-safe product.

6.10.4 Increase the probability of detection.

6.11 Design and process FMECA worksheets

6.11.1 When performing an FMECA, complete the worksheet in conjunction with the FMECA. The worksheet documents the relationship between the product design, specifications, manufacturing processes, and quality steps with the potential failure modes and effects. A design FMECA worksheet example is shown in Attachment #2, and a process FMECA worksheet example is shown in Attachment #3.

6.11.2 The design FMECA worksheet may include but is not limited to the following categories:
- 6.11.2.1 Item number
- 6.11.2.2 Functional assembly
- 6.11.2.3 Function of part
- 6.11.2.4 Root cause
- 6.11.2.5 Failure mode
- 6.11.2.6 Effect to product
- 6.11.2.7 End effect
- 6.11.2.8 Controls and preventive action
- 6.11.2.9 Detection/annunciation
- 6.11.2.10 Occurrence
- 6.11.2.11 Severity
- 6.11.2.12 Detection
- 6.11.2.13 RPN
- 6.11.2.14 Preventive/corrective actions

6.11.3 The process FMECA worksheet may include but is not limited to the following categories:
- 6.11.3.1 Item number
- 6.11.3.2 Process step
- 6.11.3.3 Description and function
- 6.11.3.4 Root cause
- 6.11.3.5 Failure mode
- 6.11.3.6 Process effect
- 6.11.3.7 End effect
- 6.11.3.8 Controls and preventive action
- 6.11.3.9 Detection/annunciation
- 6.11.3.10 Occurrence
- 6.11.3.11 Severity
- 6.11.3.12 Detection
- 6.11.3.13 RPN

6.12 Documentation

6.12.1 After the FMECA worksheets have been completed, an engineering report (ER) should be written and submitted to document control.

6.12.2 Document control will assign an ER, and a version number to the ER will be approved through the Medtronic MiniMed document approval process.

6.12.3 After the ER has been approved, this document will be maintained in document control, and any significant product and/or process changes will merit an update to the FMECA report.

Attachment #1

Numerical ratings for occurrence, severity, and detection for design FMECA

An estimated likelihood of occurrence for failures, failure modes, or cause of failure may be derived from theoretical calculations, vendor data, research data, trend analysis, and evaluation of historical nonconforming data of similar products and manufacturing

Table 1 **Likelihood of occurrence**

Description	Category (severity level)	Definition
Frequent	I (1)	Likely to occur frequently 10% or greater
Probable	II (2)	Will experience several field failures 1–9%
Occasional	III (3)	Some field failures are likely to occur 0.5–0.9%
Remote	IV (4)	Unlikely but some field failures are possible 0.2–0.49%
Improbable	V (5)	So unlikely it can be assumed occurrence may not be experienced 0.01–0.019%

processes. Actual data should be used where available. This is a subjective scale, but the scale should be fitted to the available data so no ends of the scale are left unused (Table 1).

These severity categories defined below provide a qualitative measure based on the worst case scenario for the product or process failure mode (Table 2).

The likelihood of detection rating is used to lower the rank index result if a control or detection method is proposed or inherent in the product. The severity level for detection would be lower for products that have designed fail-safe circuits, redundancy, and test circuits as part of the inherent product design (Table 3).

Table 2 **Severity categories**

Description	Category (severity level)	Definition
Catastrophic	I (1)	Likely to result in patient death
Critical	II (2)	Potential for severe injury or requires medical or surgical intervention to prevent possible severe injury.
Major	III (3)	Potential for minor injury or unanticipated surgical or medical intervention, or requires physical monitoring. Potential for system or component failure.
Minor	IV (4)	Does not meet regulatory requirements or stated performance specifications.
Negligible	V (5)	No effect on the intended function or performance of the device.

Table 3 **Detection table**

Description	Category (severity level)	Definition
Improbable	I (1)	Undetectable failure mode resulting in catastrophic device failures. Detection reliability less than 90%.
Remote	II (2)	Can be detected with special testing, not an immediate life threatening device failure, but if not corrected can become life threatening. Detection reliability equal to or greater than 90%.
Occasional	III (3)	Patient/user may become aware of problem due to some abnormal operation or unscheduled testing of the device. Detection reliability equal to or greater than 98%.
Probable	IV (4)	Always detectable during normal scheduled testing of device by physician or patient. Detection reliability less than 99.8%.
Frequent	V (5)	Failure mode is fully compensated for by redundancy or alternative operational procedure. Detection reliability less than 99.99%.

Attachment #2

Numerical ratings for occurrence, severity, and detection for process FMECA

Probability of occurrence (OCC): The probability of occurrence of a failure can be measured on a scale of 1–5. Default to the lowest ranking if the probability is unknown.

Ranking	Description	Nonconformance	Cpk
1	Very high	>10%	<0.50
2	High	≤5.0%	≥0.67
3	Moderate	≤0.25%	≥1.00
4	Low	≤0.01%	≥1.33
5	Very low	≤0.0001%	≥1.67

Severity of the effect (SEV): The severity of the effect of a failure on the patient can be defined on a scale of 1–5. Default to the lowest ranking value if severity is unknown.

Ranking	Description	Severity design	Severity process
1	Very high	Could result in death or an irreversible medical condition. • Very critical loss of therapeutic function to the patient. • Failure classifies the product as being nonconforming per our safety specifications. Patient will experience very high discomfort due to failure.	Significant injury to operator. Plant shutdown.
2	High	Could cause permanent injury. Requires intervention of healthcare professional to prevent such injury. • Critical loss of therapeutic function to the patient. • Loss is not recoverable. Specific functions of the system do not operate as expected, due to a failure in the hybrid.	Production stoppage.
3	Moderate	Could cause a reversible medical condition but would not require immediate attention of a healthcare professional to prevent permanent damage. • Semicritical loss of therapeutic function to the patient. • Loss can be recoverable. Failure is most likely noticeable and will probably cause deterioration of the system resulting in quickly shortened product life.	Production stop, unscheduled rework, minor equipment damage.
4	Low	Would not result in a medical condition but may not meet functional specification. • Very insignificant loss of therapeutic function to the patient. • The patient may notice a failure of this type but would not be dissatisfied with the effect. • Slight deterioration of the hybrid function may occur. Slow battery depletion can be expected.	Major impact on process, possible next process step more difficult, in-process rework.

Ranking	Description	Severity design	Severity process
5	Minor	No problem. • No loss of therapeutic function. This type of failure may be present, yet insignificant enough that it may not be easily observed.	Violating specification without consequences.

Probability of detection (DET): The probability of detecting a failure prior to implant can be defined on a scale of 1–5. Default to the lowest ranking value if detection probability is unknown.

Ranking	Detection	Description	Estimated probability
1	Very low	Very high likelihood that the product would be shipped containing the defect. Item is not checkable. Defect is latent and would appear at manufacturing or location (e.g., defect relates to durability of component).	<1/10
2	Low	High likelihood that the product would be shipped containing the defect. The defect is a subtle characteristic. 100% visual or manual inspection.	<1/20
3	Moderate	Moderate likelihood that the product would be shipped containing the defect. The defect is an easily identified characteristic. Automatic inspection of 100% of a variable characteristic (e.g., diameter).	<1/250
4	High	Low likelihood that the product would be shipped containing the defect. Automatic checking of 100% of a simple characteristic.	<1/1000
5	Very high	Remote likelihood that the product would be shipped containing the defect. The defect is functionally obvious and readily detected by a subsequent operation.	<1/10,000

Attachment #2

Design FMECA worksheet

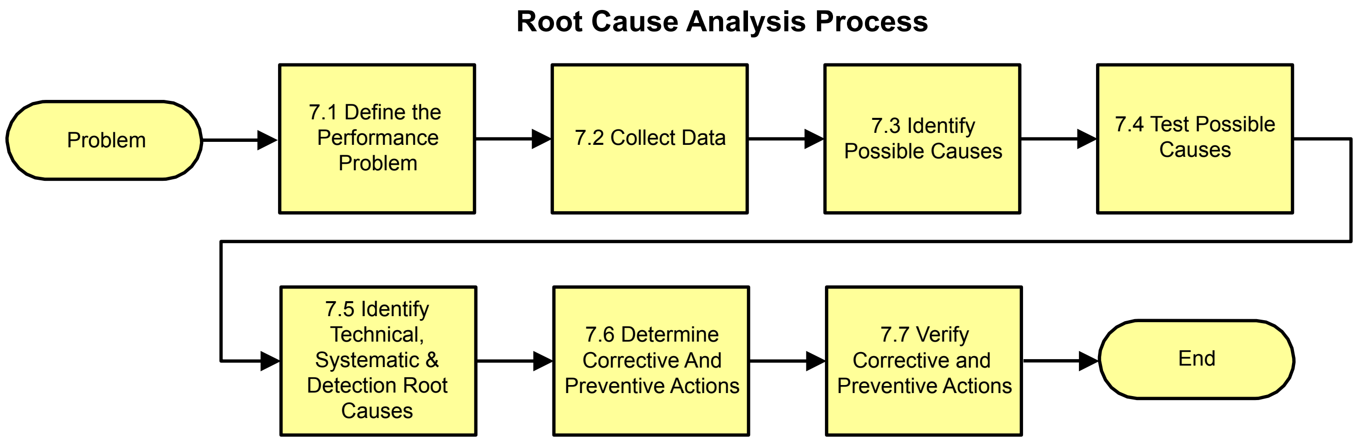
Title:			Document number:		Revision:						Sheet
Item/ step#	Description of functional assembly	Failure mode	Failure cause	Failure effect	End effect	Detection/ annunciation	Occurrence	Severity	Detection	RPN	Controls and preventive action

Attachment #3

Process FMECA worksheet

Title:				Document number:					Rev.		Sheet
Item number	Process step	Description and function	Failure mode	Failure cause	End effect	Detection	Occurrence	Severity	Detection	RPN	Controls and preventive action

Procedure example #5:
OP: RCA



1. Purpose

To define and document optional guidelines defining the methodology and tools which may be used to conduct RCA as part of CAPA investigations.

2. Scope

Root cause investigations vary with the complexity of each CAPA. In some situations, the root cause may be obvious from the outset or become obvious shortly after the investigation has begun. This procedure is optional.

3. References

3.1 21 CFR Part 820, Quality System Regulation.
3.2 ISO 13485:2003, Medical Devices—Quality Management Systems.
3.3 93/42/EEC, Council Directive Concerning Medical Devices.
3.4 SOP—CAPA system.

4. Definitions

4.1 **CAPA owner**: Biomet team member who is responsible for coordinating the CAPA report and investigation.
4.2 **Control plan:** Written description of the measures for controlling the variations in a process within the acceptable limits (businessdictionary.com).
4.3 **Correction:** A correction is the activity to rectify an identified discrepancy. An example of a correction is to reprocess a component to bring it into specification.
4.4 **Corrective action:** The implementation of solutions resulting in the reduction or elimination of the root cause of an identified nonconformity to prevent recurrence.
4.5 **Preventive action:** Proactive actions taken to prevent potential occurrences of a nonconformity and/or actions taken to assure that an identified nonconformity does not exist in other products or processes.
4.6 **Problem:** A perceived gap between the existing state and a desired state, or a deviation from a norm, standard, or status quo (businessdictionary.com).
4.7 **Root cause:** The cause or contributing factor of a nonconformity or potential nonconformity.
4.8 **Systemic root cause:** A systemic underlying cause of an identified nonconformity as it would relate to products, processes, or the quality system.
4.9 **Technical root cause**: The immediate event that caused the nonconformity to occur.
4.10 **Detection root cause**: The verification event that allowed the nonconformity to go undetected.

5. Responsibilities

In addition to specific responsibilities defined in this operating procedure (OP), the director of quality is responsible for the implementation and compliance of this OP.

5.1 The manager of QA and RA compliance is responsible for the administration of this OP.
5.2 The document/process owner, manager, and/or supervisor is responsible for ensuring that team members are aware of the work instructions needed to perform their task(s).
5.3 The CAPA owner is responsible for leading the investigation team and completing and documenting the seven steps of the investigation as described in this procedure.

6. General requirements

6.1 Per **SOP CAPA,** it is required to determine both technical and systematic root cause. The use of the methodology described in this procedure for a particular CAPA investigation is within the discretion of the manager of QA and RA compliance.
6.2 **SOP.00.04 Is/Is Not Diagram** template contains three tabs to document the investigation: "Is Is Not Measurement Plan," "Is Is Not with D & C," and "Is Is Not Test."

7. Procedure

The process describes a structured methodology for root cause analyses and CAPA processing. The overall process in graphical presentation is shown in **Appendix B**.

7.1 **Step one.** Define the performance problem.
- 7.1.1 Describe the problem using **SOP.00.04 Is/Is Not Diagram.**
- 7.1.2 The is/is not diagram will identify the process(es) under investigation.
  - 7.1.2.1 Create a flowchart of those processes.
  - 7.1.2.2 Identify inputs to each step in the process flowchart(s).
- 7.1.3 Develop **SOP.00.03 Charter Template** to identify the following:
  - 7.1.3.1 The problem statement
  - 7.1.3.2 The performance goal
  - 7.1.3.3 The team leader and member
  - 7.1.3.4 The sponsor

7.2 **Step two.** Collect data reflected by objective evidence to verify that the information in the is/is not diagram is accurate. Consider if additional or more detailed information is needed.
- 7.2.1 Update the is/is not diagram with the facts.
- 7.2.2 Any data point in the updated is/is not diagram that cannot be confirmed as factual should be so identified.

7.3 **Step three.** Develop a master list of possible causes. Consider using multiple techniques such as follows:
- 7.3.1 Using a timeline of changes.
- 7.3.2 Looking for differences within each set of is/is not data.
- 7.3.3 Identifying changes associated with any differences.
- 7.3.4 Reviewing the results of any previously prepared risk analyses relevant to the problem to identify additional possible causes.
- 7.3.5 Using brainstorming techniques such as a cause and effect diagram or brainstorming using the flow diagrams.

7.4 **Step four.** Test possible cause against the facts in the is/is not diagram.
- 7.4.1 For each possible cause, record any fact not perfectly explained as well as any assumptions that can be made to explain the fact.
- 7.4.2 If a possible cause does not fit the facts and no reasonable assumption can be made to explain the facts, the possible cause can be eliminated.

7.5 **Step five.** Identify the root cause(s).

7.5.1 Identify the technical root cause (the change).

7.5.1.1 Verify any assumptions made with the possible causes that have not been eliminated. If, with any possible cause, the assumptions made to explain a particular fact are disproved and no other assumptions can be made, this possible cause can also be eliminated.

7.5.1.2 For the remaining possible causes, appropriate testing or analysis may be necessary to further reduce the number of possible causes and identify the root cause(s). This may result in identifying new possible causes or in identifying multiple causes working together that may be causing the problem. As such, the investigation becomes an iterative process as new possible causes are identified and tested and assumptions verified or disproved. The process continues until the root cause is identified or all conceived possible causes are eliminated. The inability to find a root cause should be carefully reviewed. This should be a very rare event, but it can happen.

7.5.2 Identify any systemic root causes that contributed to the problem or allowed the problem to occur.

7.5.2.1 Once the technical root cause is known, ask "Why did this problem occur?" Additional questions include "What systems failed to prevent the problem?" and "Why did our quality system allow this to occur?" The answers to these questions are systemic root causes.

7.5.3 Identify any detection root causes that contributed to the nondetection of the problem.

7.5.3.1 Once the technical and the systemic root causes are known, ask "Why did this problem go undetected?" The answer to this question is the detection root cause.

7.6 **Step six.** Develop solutions (corrective or preventive actions) for technical, systemic, and detection root causes.

7.6.1 If the root cause identified was a mistake, error, or omission, apply mistake proofing techniques. There are normally multiple mistake proofing actions that can be taken. To decide which actions to take, consider which actions most effectively and efficiently solve the problem, including which are easier or faster to implement. These must be considered with the seriousness of the problem.

7.6.2 If the root cause identified was excessive variation or improper targeting, first reduce the variation, and then optimize the process.

7.6.3 Evaluate the corrective or preventive actions using a risk analysis approach and modify them as appropriate.

7.6.3.1 If the solution involved redesigning the product or process, include objective evidence to indicate that the actions taken do not adversely affect the finished device as required by **SOP CAPA.**

7.6.4 Develop a control plan to prevent this issue from recurring. This may include developing or revising procedures, using control charts to continuously monitor the process, or instituting quality process checks.

7.6.5 Implement the identified solution(s) (CAPA) and the control plan.

7.6.6 Update the applicable risk analysis to include any previously unrecognized failure modes and possible causes learned during the investigation.

7.6.7 Disseminate information regarding the problem, root causes and CAPA to other appropriate functions of the organization to prevent those problems from occurring as required by **SOP CAPA.**

7.7 **Step seven.** Verify the solution (verification of effectiveness [VoE]).

7.7.1 Verify the effectiveness of the CAPA and control plan for a sufficient period of time to assure performance is restored and that the control plan is effective.

7.7.1.1 If performance does not improve, the root cause has not been identified.

7.7.1.2 If the performance is only partially improved, one or more additional root causes may exist or the solution was not as effective as expected.

7.7.1.3 In either case, the investigation should continue pursuant to **SOP CAPA.**

8. Revision history

Revision	Description of change
1	New OP

Procedure example #6:
SOP: quality system data analysis

1. Purpose

To define and document an OP for collecting and analyzing quality system data from ABC's products and processes, to assure the suitability and effectiveness of the quality management system, and to identify opportunities for improvement.

2. Scope

Data collection and analysis performed by ABC to review performance measurements of the quality system.

3. References

3.1 External standards

3.1.1 21 CFR Part 820, Quality System Regulation.

3.1.2 ISO 13485:2003, Medical Devices—Quality Management Systems.

3.1.3 ISO 14971, Application of Risk Management to Medical Devices.

3.1.4 93/42/EEC, Council Directive Concerning Medical Devices.

3.2 Company documents

3.2.1 Quality policy and objectives

3.2.2 Risk management

3.2.3 Internal quality audits

3.2.4 CAPA system
3.2.5 Quality systems reporting
3.2.6 CAPA trigger matrix
3.2.7 Management review

3.3 Forms
3.3.1 None

4. Definitions/abbreviations

4.1 **Corrective and preventive action:** Actions to correct and prevent nonconformities under the CAPA.

4.2 **Data owner:** Team member most responsible for the information that is utilized to measure quality of products and processes.

4.3 **Quality management system:** The organizational structure, responsibilities, procedures, processes, and resources for implementing quality management.

4.4 **Quality record:** Any written, electronic, or automated document generated to demonstrate conformance to specified requirements and achievement of the quality management system.

4.5 **Quality plan:** A plan to identify and address the activities and resources required to facilitate and ensure that the quality requirements for a specific product, project, process, contract, or venture are met and implemented.

4.6 **Quality scorecard:** A document that tracks performance of quality objectives through quality indicators. Several indicators have a specified goal and alert limit to help define performance levels that are considered to have triggered.

5. Responsibilities

In addition to specific responsibilities defined in this OP, the director of quality is responsible for the implementation and compliance of this OP.

5.1 Quality and regulatory compliance manager is responsible for the administration of this OP.

6. General requirements

6.1 N/A

7. Procedure

7.1 Quality system data analysis objectives

7.1.1 Collection and analysis of data should be conducted for feedback on whether customer requirements are being met, to determine the suitability and effectiveness of the quality system, to determine whether processes for realization of products and services conform to requirements, and whether opportunities exist to improve the quality of processes, product, and services.

7.1.2 Data should be collected from multiple sources to determine the status and effectiveness of the quality management system at several levels.

7.1.2.1 At the business level, key indicators are used to determine whether quality objectives are being achieved and internal audits assess the suitability and effectiveness of the quality management system.

7.1.2.2 At the process level, data is analyzed from specific product and process monitoring sources as defined in SOP ZXX, quality systems reporting.

7.1.2.3 At the work station level, routine monitoring of key parameters should be planned and implemented as required by an approved control plan, quality plan, or protocol.

7.1.2.4 Analysis of source quality data will include global analysis across all source CAPA data lines (i.e., analysis of common factors, such as problem, product, lot number, staff, and other criteria against all corresponding source CAPA data, including quality complaints, nonconformances, internal and external audits, and CAPA reports) to identify any additional existing and potential quality problems.

7.1.3 Data collection should be planned as follows:

7.1.3.1 Data owners may report independently within their department or through interface with the QA/regulatory compliance group.

7.1.3.2 The QA/regulatory compliance department is responsible for publishing CAPA trigger matrix meeting reports in support of the quality scorecard. This effort involves direct interface with data owners who may provide data collection requirements and who may provide comments needed for management review of adverse trends.

7.1.3.3 Meetings are held monthly to review quality indicator results with emphasis on areas that fail to achieve targets or that have unfavorable trends.

7.1.3.3.1 The CAPA trigger matrix meeting will review all applicable quality scorecard indicators from all applicable ABC facilities per SOP ZXX, quality systems reporting.

7.1.3.3.2 Data owners from each ABC location are responsible for providing quality data to the ABC regulatory compliance department who is hosting the CAPA trigger matrix meeting.

7.1.3.4 The data owners for these indicators are expected to provide/present the results of any assessment of the problem areas and the actions they have taken to bring about improvement.

7.1.3.5 Where appropriate, the status of any implemented corrective actions will be reviewed to communicate the results in addressing a previously triggered indicator.

7.1.4 Possible changes to the quality scorecard will be reviewed semiannually during the management review meeting and on an as-needed basis.

7.1.4.1 Proposed changes require acceptance from the data owner.

7.1.5 A report covering internal audit results is collected and distributed per OP ABC, internal quality.

7.2 Data analysis should be planned as follows:

7.2.1 Appropriate statistical methodology should be employed where necessary to detect and address recurring quality problems.

7.2.2 The need for correction and corrective actions will be determined when a quality indicator has triggered, where a risk assessment determines that action must be taken or while conducting a review of each quality indicator's trend during the CAPA trigger matrix meeting.

7.2.2.1 In addition, management may also initiate a CAPA request for items they determine significant. The ultimate decision for initiating a CAPA rests with the senior quality manager or designee as referenced in SOP for corrective and preventive action system.

7.2.3 Quality system data analysis records should be maintained with the associated quality record per SOP for control of records where applicable. Each department that generates reports per this procedure will maintain a master file of standard data analysis reports generated for product, process, and quality system monitoring not associated to specific quality records. These records should be permanent unless otherwise determined by executive management.

8. Record keeping

8.1 For ABC, records of new pending documents and existing (approved) documents, current change requests and logs, peer review logs, action items, and review records are housed electronically in the ABC database system, document control module. Records of previous revisions of documents, completed (obsolete) change requests and logs, obsolete review records, and obsolete documents are housed electronically in the database, document control archive module.

Conclusion: requirements for an effective CAPA program

Root cause analysis (RCA) helps identify what, how, and why something happened, thus preventing recurrence. Root causes are underlying, are reasonably identifiable, can be controlled by management, and allow for generation of recommendations.

The process involves data collection, RCA charting, root cause identification, recommendation generation, and implementation of corrective and preventative actions.

Regulatory concerns

CAPA is also a major area of regulatory concern for both the FDA and ISO.

- They have recognized that how a quality system is maintained and monitored is critical to its effectiveness—i.e., learn from CAPA issues to improve the QA system.
- Their risk-based CAPA requirements demand a well-documented system.

The CAPA subsystem of a company's quality system is nearly always examined during FDA and ISO regulatory compliance audits. Unfortunately, many companies do not implement CAPA as effectively as they could, and 30% to 50% of nonconformances cited are directly due to CAPA violations.

The CAPA procedure

- The CAPA procedure should include procedures for how the firm will meet the requirements for all elements of the CAPA subsystem.
- Does a system for the identification and input of quality data into the CAPA subsystem exist?
- If so, does such data include information regarding product and quality problems (and potential problems) that may require corrective and/or preventive action?
- Summary
- The FDA cannot dictate the degree of action that should be taken for quality problems, but they do expect companies to have *plans in place for the investigation of problems, for determining the probable causes, and for implementing corrective actions.*
- The effectiveness of these actions also needs to be monitored and reviewed on a timely basis!
- Look for similar trends!

The FDA will not dictate the degree of action that should be taken to address a quality problem, but they do expect companies to have plans in place. They expect companies to address how they will perform their investigations, how they will determine probable root cause or causes, and how they will implement corrective actions. What is more important, the FDA will follow-up to see that the plans that are in place are effective.

Remember that corrective action is a reactive tool for system improvement to ensure that significant problems do not recur. Both quality systems and the CGMP regulations emphasize corrective actions. However, a greater emphasis should be placed on the preventive action program so that we can identify and prevent any quality and product issues before failure occurs.

Quality systems approaches call for procedures to be developed and documented *to ensure that the need for action is evaluated relevant to the possible consequences, the root cause of the problem is investigated, possible actions are determined, a selected action is taken within a defined timeframe, and the effectiveness of the action taken is evaluated.*

Communication

Another very important aspect will be that you communicate with folks who are close to the problem and who will be using the new procedures involved in the events in the investigation. Do this so that people know what has happened. The people who are most closely related to the process should understand what has been done to address the issues. This gives you an informed, educated manufacturing team. People who are respected and given the information they need to do their work perform better, have better attitudes, and generally are more satisfied workers.

All that information is going to be symptom management, with the management review criteria and the need for review of CAPA, from the pharma side and the annual product review (APR) process as well. We are looking at nonconforming deviations here, and all such information is to be reviewed by management. This is another thing the FDA will be looking for: has management been properly apprised of ongoing manufacturing situations?

It is not just the verification that must be done. It is not merely the follow-up that must be completed, but also the communication of these changes that must occur. Communicate the changes—whether they are procedures, equipment changes, manufacturing, or environmental changes. All of these should be communicated to the folks who are directly responsible and to those who work with the systems and processes. The information should also go to management, so we have a closed-loop system. This way, everyone will be properly informed.

Trends

Make certain that you look at the right inputs. We want to make certain that we look at the sources of information that are going to give us well-rounded information on the quality system, to understand whether we have issues in testing or whether we have issues in vendor performance in our recurring rejection or recurring quarantine of incoming products due to complaints.

When you start looking at your CAPA program, and you begin observing the trends, you will probably see clusters of data. You will be able to see more of the big picture—that you actually do have recurring issues. Seeing this data, you should take a more serious approach to the problem. Eventually, as you continue to trend your data, you will not (and should not) wait until you see data clusters. As you analyze the data on a routine basis, take the actions you need to as they become apparent to you.

Another important thing, from a device perspective, would be that if you see problems recurring, link these corrective actions to other systems. For example, a design change occurs because there is a new use for the product that was not originally intended. There may be a need to change the product design to address the new issue. If our users are using the product incorrectly, are we changing the labels? We have handled product complaints; now we have significant new data. What are we doing with this information? Are we linking it to other systems to make sure that the problem uncovered by the complaints is being addressed at all levels, in all divisions within the company? Set up the CAPA system such that all aspects of the quality system are linked and "talking to each other." This type of data should be captured and put to immediate use in other relevant areas.

Always look at the analysis of data. If there are recurring issues in areas that previously have been identified for corrective action, then the corrective action was not effective. That means you are taking the Band-Aid approach. That means you need to analyze again for the correct root cause. Trending will give you the information you need. Trending will show whether the system is steadily improving or whether your actions are effectively Band-Aid issues rather than directly addressing the root cause.

The best indicator of how a product is performing in the market is the level of complaints; listen to the voice of your customers. That is the prime feedback mechanism from our customers on how happy or unhappy they are with the product's effectiveness. Why are they complaining? What are our products doing, and are we learning from these complaints? Are we learning and changing our products because, perhaps, we did not take into consideration certain aspects that should have been changed from the initial design review or from the initial design development of a process?

Make sure that you look at the complaint data. When the FDA comes into your facility, they will challenge your data. They are going to see whether you are looking at all of your data, and they will observe the things you are looking at. Do the procedures identify everything that you are going to look at? When will you be looking at the trending of the items, the nonconforming issues, the complaints, the MDRs, the adverse event reports? Make sure that you are looking at those quality indicators so that you can take appropriate corrective action on a timely basis. The authorities will want to know that the information is accurate, complete, and timely. The agencies will verify and confirm that the company is taking the right actions and note when the actions are being taken.

Promote improvement

- CAPA = continuous quality improvement.
  - Continuous quality improvement is an important goal for most businesses, and troubleshooting and resolving problems is a typical activity in that process.
  - The reason is obvious: problems have a financial impact on the company.

- A CAPA system is an essential management tool that should be a part of every quality system.
- It can help assure continuous quality improvement and customer satisfaction.

The effectiveness and efficiency of the quality system can be improved through the quality activities described in the FDA's new guidance. Management may choose to use other improvement activities as appropriate. However, *it is critical that senior management be involved in the evaluation of this improvement process.*

One aim is to get Quality to support continuous improvement—that is another thing the FDA and the ISO auditors will be looking for. As you perform the risk analysis, prioritize according to the impact of each. Select those issues to work on first that have major impact upon product or patient. Within the CAPA program, CAPA will not be effective unless you have a solid root cause analysis program. You need to understand and identify the causes. It may be more than one cause that produced the problem. Once you have identified those things, you can analyze and appropriately determine what the corrective actions should be.

Another major issue from a regulatory perspective is that we should be learning from the CAPA issues that arise. We should be learning from our mistakes. We should be using those things that continuously failed and that were monitored to see whether there was a trend. Then we should follow through to see if we have actually improved a process or procedure as the result of doing a review or if we are using a Band-Aid approach.

Procedural imperatives

The FDA will be looking to see how we collect information, how we analyze information, how we identify what we are going to look at, how we identify when we will be investigating or not, and the kinds of quality problems we plan to look at. They will investigate whether we are looking at all the quality inputs we are supposed to be looking at. All our discoveries should be documented. They will be looking at our procedures to discover whether we have objective evidence to show that the system is working—that we are, in fact, identifying the recurring issues from a practical perspective, and that from a reactive perspective, we have identified the corrective actions.

Proactive focus

From a preventive action point-of-view, the agency will look to see whether you are considering proactive preventive actions. They will ask you, or other representatives of the company, what activities the company is involved in from a preventive action standpoint. Be prepared to respond. Think about some of the analyses that you do. For example, a simple tool most of us use involves statistical techniques. Sometimes we use SPC charts to monitor progress, process, or process controls. That is part of preventive, proactive thinking. When we use statistical techniques we are planning on not failing. We are looking at trends and shifts in the production environment, which is another way of looking at preventive planning that can be identified and monitored over time.

In these matters as well, we need to communicate to the folks who are responsible. Sometimes the important information does not get to management, and when management has to react to a problem, they are not even aware that there is a problem. Management needs to be aware of these issues, so they can effectively deal with quality, product, and process issues to prevent them from recurring. They need us to keep them informed.

Learning from prior failures

Once we begin applying what we learn each time we fail, we should begin to see continuous improvement. In any quality system, we must continually look at how we will improve as a result of the lessons we have learned from our corrective actions. As we learn from these changes, the problems will disappear. If the same issues recur, and we take the same corrective Band-Aid approaches, then we are not improving. If this happens, we will be in constant firefighting mode.

When we strive for continuous improvement, we concentrate on those efforts that have resulted from corrective actions and from our audits. We learn from our mistakes. In the process of continuous improvement, we must include risk assessment. That is one thing that both the FDA and the European agencies are looking for. To implement risk-management approaches into the evaluation of failures includes determining whether the failures are so critical that they could have patient or product impact. If patient or product implications could be a factor, raise the question; find out what is being done, on a timely basis, to address those things that are most critical.

Considering risk impact

Investigators want to have the assurance that we, as companies that manufacture medical devices and pharmaceutical products, understand that if we have issues in production that we will perform risk assessments to understand and prevent failures from occurring again. They want to know that we can tell the difference between critical and noncritical issues, and that we are willing to make the judgments that differentiate the two. It is the consideration of the impact, criticality, and severity of these facts that may have an impact on the patient or product that is one of the chief concerns of agency inspectors.

Root cause analysis helps identify what, how, and why something happened, thus preventing recurrence. However, unless an effective CAPA system is in place, and people who need to use this system truly embrace it, the implementation of corrective and preventative actions may not prevent nonconforming issues from recurring!

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Normative references

ISO 9001:2000.
ISO 13485:2003.
Section 8.5.2 Corrective actions.
Section 8.5.3 Preventive actions.
ISO 14001:2004.
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21 CFR 820 – Quality system regulation.
820.100 Corrective and preventive action.

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Glossary

483 FDA form for listing observations.
APR Annual product review.
CAPA review A review under the umbrella of the CAPA system conducted by dedicated members of the site management to determine if quality events are being reliably identified, investigated, and corrected. This review includes the review of CAPA reports to determine if preventive actions are required and if additional investigations and/or corrective actions need to be initiated and performed.
CAPA review board (CRB) A review under the umbrella of the CAPA system is conducted by dedicated members of the site management to determine if quality events are being reliably identified, investigated and corrected. The board reviews the trend analysis from the different quality data sources to determine if preventive actions are required and if additional investigations and/or corrective actions need to be initiated and performed.
Complaint Any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution [Federal Regulations 21 CFR—Part 820.3].
Corrective action (CA) An action taken to eliminate the cause of an existing nonconformity, defect, or other undesirable situation in order to prevent recurrence.
Corrective and preventive action (CAPA) process A systematic approach to review in-process quality data, post-market surveillance, and all other nonconformance information to identify, investigate, prevent, and correct quality issues.
Critical event An event that has resulted in or contributed to a problem leading to a failure resulting in a severity level 1.
Critical requirements Those process or product requirements that, if not met, would be associated with a failure mode of severity level 1.
Design FMECA Use of FMECA to analyze the potential failure modes of the product design.
Designated personnel Those individuals who have been appointed by management to perform a specified activity (e.g., nonconformance review board, CAPA review board, risk-evaluation team).
Detectability The potential of a defective product reaching the end user without being detected.
Detection Detection of problems prior to distribution, or by the customer before damage occurs.
Distributed products Everything that could be used by the customer (e.g., finished products, spare parts, software upgrades, labeling material, user and service manuals).
End effect An adverse consequence that a failure mode has on the function of a device.
Evaluation Gathering information and reviewing the facts surrounding an event to understand the problem. An evaluation can be used to determine the need for further investigation or risk analysis.

Event A potential problem that may affect the quality of a product or the suitability of a material, system, operation, process, document, equipment, or program that is part of the quality system. Events may be identified via the CAPA system including complaints, quality system nonconformances, DMR nonconformances, results of CAPA reviews, and results of management reviews.
Executive management Management with authority to make changes to the quality system.
Failure mode The way in which a product or process could fail to perform its desired function.
Failure mode, effects, and criticality analysis (FMECA) A procedure by which each potential failure in a system is analyzed to determine the results or effects thereof on the system and to classify each potential failure according to its severity.
FDA Food and Drug Administration.
Hazard Potential source of harm.
Investigation A planned and documented analysis of events and circumstances contributing to a problem to determine the cause of the problem and the most appropriate corrective and/or preventive action(s). May involve any combination of experiments, testing, review of data, statistical analysis, interviews, expertise, and product inspection.
Major event An event that has resulted in or contributed to a problem leading to a failure resulting in a severity level 2.
Major requirements Those process or product requirements that, if not met, would be associated with a failure mode of severity level 2.
Manufacturing material Any material or substance used in or used to facilitate the manufacturing process, a concomitant constituent, or a by-product constituent produced during the manufacturing process, which is present in or on the finished device as a residue or impurity not by design or intent of the manufacturer.
MDR Medical device record.
Minor event An event that has resulted in or contributed to a problem leading to a failure resulting in a severity level 3.
Minor requirements Those process or product requirements that, if not met, would be associated with a failure mode of severity level 3.
Negligible event An event that has resulted in or contributed to a problem leading to a failure resulting in a severity level 4.
Nonconformance Any noncompliance with a device master record or the quality system.
Nonconformity Defect or other undesirable situation. Example: Corrective actions identified as a result of a nonconformance for one product are PAs when implemented to prevent a similar nonconformance in another product.
Occurrence The likelihood (probability) that a specific failure mode, which is the result of a specific cause and which is under current control, will happen.
Preventive action (PA) Action taken to eliminate the cause of a potential nonconformity, defect, or other undesirable situation in order to prevent occurrence. Example: Corrective actions identified as a result of a nonconformance for one product are PAs when implemented to prevent a similar nonconformance in another product.
Probability The likelihood of an event (occurrence).
Process effect All the effects of each failure mode including current step effects and downstream subassembly effects.
Process FMECA Process FMECA is to analyze the potential failure modes of the manufacturing processes that build the product.
Product Components, manufacturing materials, in-process devices, finished devices, and returned devices.
QSIT Quality system inspection technique.

Quality data sources The systems and processes that provide conforming and nonconforming inputs to the CAPA system.

Quality review board (QRB) QRB members are appointed by executive management and represent quality assurance and/or quality control, manufacturing, engineering, and regulatory affairs.

RCAR Root cause analysis report.

RCAT Root cause analysis team.

Remedial action Action to immediately resolve a specific issue resulting from a complaint or nonconformance.

Risk priority number (RPN) A mathematical product of the numerical severity, occurrence, and detection ratings ($RPN = (S) \times (O) \times (D)$).

Root cause One of multiple factors that set in motion the cause and effect chain that creates a problem and, if eliminated or modified, would have prevented the undesired outcome.

Root cause analysis (RCA) A structured evaluation method that identifies the root causes for an undesired outcome and the actions adequate to prevent recurrence.

Potential root cause: A root cause that theoretically can create/contribute to create a problem.

Confirmed root cause: A root cause for which evidence has been provided that it created/contributed to create a problem.

Severity Estimate how severe the effect of this failure is on the end user. Severity is the factor that represents the seriousness of a failure to the customer after it has occurred.

Standard operating procedure (SOP) Procedures are a set of step-by-step instructions to achieve a predictable, standardized, desired result often within the context of a longer overall process.

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SUBCHAPTER C – DRUGS: GENERAL

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Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulation – Pharmaceuitical, Biologics, Compounding Products, OTC Products (Over the Counter Drugs) http://www.fda.gov/downloads/Drugs/.../Guidances/UCM070337.pdf.

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'*Note*: Page numbers followed by "f" indicate figures, "t" indicate tables, and "b" indicate boxes.'

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WOODHEAD PUBLISHING SERIES IN BIOMEDICINE

CAPA in the Pharmaceutical and Biotech Industries contains the most current information on how to implement, develop, and maintain an effective Corrective Action and Preventive Action (CAPA) and investigation program using a nine step closed-loop process approach for medical devices and pharmaceutical and biologic manufacturers, as well as any anyone who has to maintain a quality system.This book addresses how companies often make the mistake of fixing problems in their processes by revising procedures or, more commonly, by retraining employees that may or may not have caused the problem. This event-focused fix leads to the false assumption that the errors have been eradicated and will be prevented in the future. The reality is that the causes of the failure were never actually determined, therefore the same problem will recur over and over. CAPA is a complete system that collects information regarding existing and potential quality problems. It analyzes and investigates the issues to identify the root cause of nonconformities. It is not just a quick-fix, simple approach, it is a process and has to be understood throughout organizations.

Key features include:

- provides an understanding of the principles and techniques involved in the effective implementation of a CAPA program, from the identification of the problem, to the verification of preventive action
- emphasizes the practical aspects of how to perform failure investigations and root cause analysis through the use of several types of methodologies, all explained in detail
- explores effective methods to use with a Corrective Action system to help quality professionals identify costly issues and resolve them quickly and appropriately

Jackelyn Rodriguez is the President of Monarch Quality Systems Solutions, a consulting firm in New Jersey, and she is currently serving in a technical and regulatory compliance consultation capacity for several Medical Device, Pharmaceutical, Biologics, OTC Cosmetics and Compounding Pharmacy companies. Her consulting services place emphasis on all aspects of Quality Systems and Systems-based Implementation & Auditing, FDA Mock Inspections and Implementation of Risk Based programs. She has over 32 years of experience in all facets of Quality Assurance and Regulatory Compliance. She specializes in U.S. Regulations and International Standards, which include FDA's QSR/GMPs 21 CFR Part 820, Parts 210 & 211, 503A 503B, 600 and Part 11 as well as ISO 9001/2000, 13485/2003, MDD/IMDD requirements, Canadian Regulation requirements, JPAL' MO no. 169 for Medical Device, Pharmaceutical and Biologics Industry. Her expertise encompasses Lean Manufacturing and Six-sigma Investigations and CAPA, Auditing, Process Validation, Document Control, Electronic Records/ Electronic Signatures and Documentation Systems, Training and Learning Management Systems, Supplier Quality Assurance systems implementation, Quality Engineering, CE-Marking, Design Controls, Technical Files compilation, Risk Management/Hazard Analysis, Post-Market Surveillance and Vigilance as well as HIPAA requirements. Ms. Rodriguez has been responsible for the creation and implementation of entire Quality Systems for numerous Device and Pharmaceutical companies. In addition to the above, Ms. Rodriguez also possesses extensive knowledge of Compliance-Inspections and facilitating responses to address FDA-483s and Warning Letters.

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