

CAPA for the FDA-Regulated Industry

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Dedication

*This book is dedicated to my wife Norma and
my son José Andrés. Their continuous support
and love made this book possible.*

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Preface

Medical devices, biopharmaceutical, and traditional drug manufacturing companies devote an important part of their resources to dealing with incidents, investigations, and corrective and preventive actions. The corrective and preventive action system is known as the CAPA system. The CAPA system is second to none in terms of frequency and criticality of its deviations, and most of the regulatory actions taken by the FDA and foreign regulators are linked to inadequate CAPA systems. This guidance book provides useful and up-to-date information about this critical topic to thousands of engineers, scientists, and manufacturing and quality personnel across the life sciences industries.

Understanding the CAPA system is a fundamental prerequisite to improving it. Investigating and discovering the root cause of any event is just the starting point of the CAPA journey. After that, we must develop and implement adequate and effective corrective and/or preventive actions. A formal process must be established to evaluate how well implemented actions prevent the recurrence of those causes. Although preventive actions are half of the CAPA system, many companies do not have any true preventive actions. Understanding and improving the corrective and preventive actions system as a whole is the focal point of this book, the first of its kind dealing exclusively with this critical system within this highly regulated industry.

These pages evolved from hundreds of training sessions I have conducted as a consultant to dozens of regulated companies. By reviewing CAPA systems of nearly one hundred manufacturing plants (pharmaceuticals, medical devices, biological products, and food manufacturing), I developed firsthand awareness of the real issues of the CAPA system. These are addressed in this book in the form of a decalogue, a set of ten basic rules. Thus, the objective of this book is to help these industries improve their CAPA systems and succeed in their mission of producing safe and effective products.



Chapter 1 establishes the relationship between the CAPA system (identification, investigation, and fixing of problems) and the quality system environment. It also includes the most important definitions and concept of the CAPA world. I strongly recommend you begin by reading and understanding those critical concepts. Many people involved in developing and implementing corrective and preventive actions have trouble providing correct definitions of those concepts.

Chapter 2 describes the current requirements and regulations by type of products and by country (U.S., European Community) and by international harmonized documents. It also includes a review of ISO 13485:2003 requirements as they apply to medical device manufacturers as well as a review of the recent international guidance on CAPA for medical devices published September 2009. This chapter finishes with an overview of the current FDA regulatory trends related to the CAPA system.

Chapter 3 describes sequentially the entire CAPA process. It starts with problem detection, continues with root cause investigation, generation, and implementation of corrective and preventive actions, and ends with the evaluation of their effectiveness and the management of the CAPA system. Topics such as trending, evaluation of training effectiveness, and risk management concepts and their relation to CAPA are discussed in this chapter. Special emphasis is dedicated to the investigation of so-called “human error.”

Chapter 4 contains useful hints to properly document the elements of the CAPA process.

Chapter 5 describes a decalogue containing the ten most common opportunities found in the CAPA system and how to fix them. Real examples are analyzed and best practices are discussed for each.

Chapter 6 presents the basic elements to be included as part of an internal CAPA expert certification, which is one of the recommended ways to reinforce your CAPA system.

Chapter 7 includes several forms that can be used as templates during failure investigations, development of corrective and preventive actions, and evaluations of effectiveness. These forms include dozens of questions that provide guidance and are a great help during the process of investigation and generation of effective actions to avoid the recurrence of unwanted situations. Also included is a form to be used when investigating human errors.

Finally, Chapter 8 presents a list of key recommendations to improve your CAPA system.

1

The Quality System and CAPA

1.1 THE QUALITY SYSTEM AND CAPA

A quality system is a set of formalized business practices that define management responsibilities for organizational structure, processes, procedures, and resources needed to fulfill product or service requirements, customer satisfaction, and continuous improvement. A quality management system (QMS) is a set of interrelated elements (processes) used to direct and control an organization with regard to quality. In other words, a quality system dictates how quality policies are implemented and quality objectives are achieved.

Continuous improvement is the result of ongoing activities to evaluate and enhance products, processes, and the entire quality system to increase effectiveness. The organization must continuously improve the effectiveness and efficacy of its QMS through the use of its quality policy, quality objectives, audit results, analysis of data, corrective and preventive actions, and the management review processes.

Analyzing data is an essential activity for any possible improvement at any level (system, process, and product/service). The organization must collect and analyze appropriate data to demonstrate the suitability and effectiveness of the QMS. This must include data generated as a result of monitoring and measurement and from other relevant sources. The analysis of data will provide information on customer satisfaction, conformity to product or service requirements, trends of processes and products including opportunities for preventive action, and suppliers.

Corrective action is one of the most important improvement activities. It identifies actions needed to correct the causes of identified problems. It seeks to eliminate permanently the causes of problems that have a negative impact on systems, processes, and products. Corrective action involves finding the causes of some specific problem and then putting in place the necessary actions to avoid a reoccurrence. Preventive actions are aimed at preventing the occurrence of potential problems. Correction of the problem is the third basic element of the corrective and preventive

action system. These efforts attack symptoms rather than causes and sometimes are mentioned as immediate, remedial or containment actions.

The concept of CAPA is not restricted to any particular industry or sector. It is a widely accepted concept, basic to any quality management system. Since quality systems strive to continuously improve systems, processes, and products/services, there must be mechanisms in place to recognize existing or potential quality issues, take the appropriate steps necessary to investigate and resolve those issues, and, finally, make sure the same issues do not recur. Processes of the life sciences regulated industries (the manufacturing of medical devices, biopharmaceuticals, and traditional drugs) are plagued with deviations and nonconformities. Worldwide regulatory agencies perform thousands of inspections every year; often CAPA system violations are at the top of the list.

Within the United States, lack of adequate investigations, no true root cause analysis, lack of effective corrective actions, and lack of true preventive actions are common findings pointed out by Food and Drug Administration (FDA) inspectors. As evidenced by the significant number of problems related to this issue, companies are facing many challenges in making the CAPA system work as intended. Life sciences regulated companies must ensure that their CAPA system looks beyond product issues and considers other quality issues including problems associated with processes and systems. Unfortunately, a significant number of regulated companies are approaching the CAPA system very lightly, implementing corrections but no true corrective and preventive actions.

CAPA systems are inherently data driven. Without adequate, relevant data, it can be difficult to draw definitive conclusions about systems, processes, or product quality issues. One of the challenges many companies face is the proliferation of uncorrelated data repository systems within the organization. A typical example for U.S. companies is the existence of two separate systems (domestic and foreign) for investigating customer claims. Another example is the lack of relationship between supplier and internal CAPA systems. By having a correlated CAPA system, a company will be better able to diagnose the health of its quality system and will have a better chance of recognizing and resolving important quality issues.

As the quality system within an organization matures, there should be a natural shift in emphasis from corrective action to preventive action. Issues that must be corrected usually become obvious. However, issues that have the potential for becoming a problem are less readily recognized. How can a firm pore over its internal data to find those few situations that might be the precursors of problems down the road? The answer is part of the regulations. Companies must establish methods to evaluate both the *nonconformance* data (which will feed the corrective action portion of the system) and the *in-conformance* data (which will be the basis of preventive actions).

An effective CAPA system must be a *closed loop* system. This term refers to at least two elements of the CAPA system. First, it means there are sufficient controls in place to ensure that the CAPA process runs through all the required steps to completion, and that management and those responsible for quality have visibility and input to the process. In addition, top management must review the outputs of the CAPA system. Very often companies focus on completing the individual tasks of a particular corrective action, yet lose track of the original purpose of the CAPA system. For example, a particular product problem may be resolved, but no evaluation is ever performed to ensure that the solution was effective. In this example, the loop was never closed.

Second, a good CAPA system closes the loop on many of the documented issues by directly providing input into basic elements of the QMS such as design control. For example, nonconforming product procedures are directed at assuring that the nonconforming product is identified and corrected prior to distribution or prevented from being distributed. Frequently, a correction or temporary change will be implemented to assure that the affected material is fixed. An effective CAPA system will require that the problem be investigated and its root causes effectively attacked with the appropriate corrective actions.

A documented procedure for CAPA must define requirements for the following elements:

1. Collect and analyze quality data to identify existing and potential causes of nonconforming products or other quality problems.
2. Investigate the causes of existing and potential nonconformities.
3. Identify corrective and preventive actions.
4. Verify or validate corrective and preventive action prior to implementation.
5. Implement corrective and preventive actions.
6. Evaluate the effectiveness of corrective and preventive actions.
7. Ensure that the information related to quality problems or nonconforming products is disseminated to those directly responsible for assuring the quality of such product or the prevention of such problems.
8. Submit relevant information on identified quality problems, as well as corrective and preventive actions, for management review.

Finally, all CAPA system activities, and all quality system activities in general, must follow a risk-based approach. Because all existing and potential problems do not have the same importance and criticality, the prioritization of actions must correlate with the risk and the magnitude of each situation.

The four key CAPA definitions are:

- **CAPA (corrective and preventive action):** A systematic approach that includes actions needed to correct (correction), avoid recurrence (corrective action), and eliminate the cause of potential nonconforming product and other quality problems (“preventive action”).
- **Correction:** Action to eliminate a detected nonconformity. Corrections typically are one-time fixes. A correction is an immediate solution such as repair or rework. Corrections are also known as remedial or containment action.
- **Corrective action:** Action to eliminate the causes of a detected nonconformity or other undesirable situation. The corrective action should eliminate the recurrence of the issue.
- **Preventive action:** Action to eliminate the cause of a potential nonconformity or other undesirable potential situation. Preventive action should prevent the occurrence of the potential issue.

1.2 CAPA RELATIONSHIP WITH OTHER QUALITY SUBSYSTEMS

The CAPA system is a critical component of an effective QMS and it must maintain a close relationship with other quality subsystems (as depicted in Figure 1.1). The ultimate goal of any regulated company must be to have a CAPA system that is compliant, effective, and efficient. All relevant subsystems that may produce nonconformances must be part of the process.

There are multiple feeders to the CAPA system, both internal and external to the company (as represented in Figure 1.2). Internal processes encompass both *nonconformance* and *in-conformance* results, internal audits and assessments, management reviews, and so on. External sources of CAPA process inputs are supplier audits and assessments, customer feedback, and results from external audits and assessment such as regulatory agencies, ISO, and so on. A detailed discussion of those feeders can be found in Chapter 3.1.1

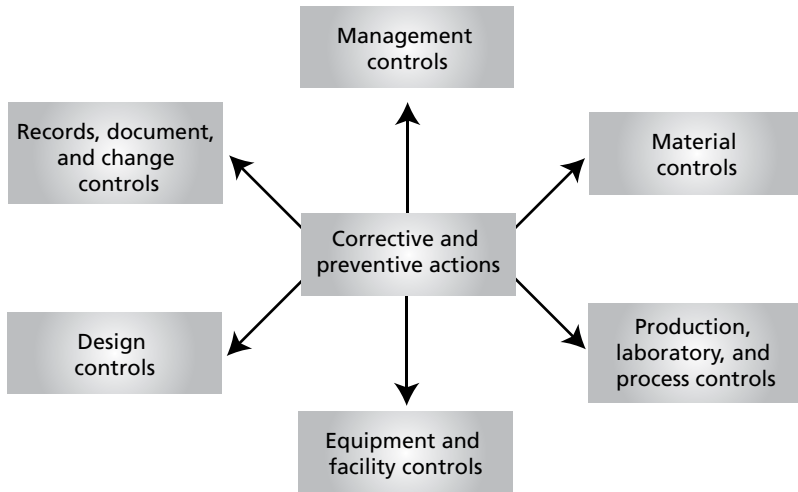


Figure 1.1 The CAPA system and the manufacturing quality system.

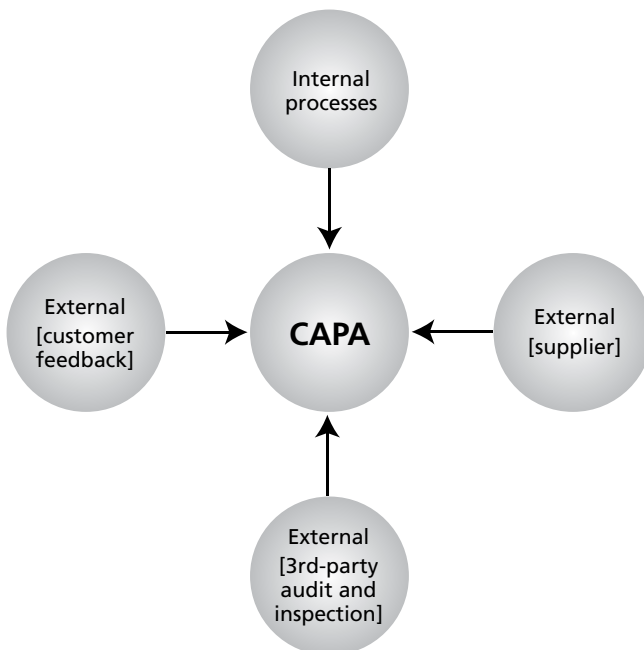


Figure 1.2 Feeders of the CAPA system.

1.3 CORRECTIVE OR PREVENTIVE?

One of the most sterile debates one can witness is the discussion between two CAPA professionals about whether a specific action they are working on should be considered corrective or preventive. The debate is pointless because what really matters is whether the action would attack a root cause.

To add even more confusion, one need only read the formal definition of corrective action. ANSI/ISO/ASQ Q9001-2008 section 8.5.2 defines corrective action as “action to eliminate the causes of nonconformities in order to *prevent* recurrence.” ANSI/AAMI/ISO 13485-2003 contains the same definition, and the FDA regulation for medical devices (Title 21 CFR §820.100) establishes that each manufacturer shall identify “the action(s) needed to correct and *prevent* recurrence of nonconforming product and other quality problems.” They use the word *prevent* as part of the *corrective action* definition.

To avoid any confusion, the word *prevent* is replaced by the word *eliminate* throughout this book; the definition of *corrective action* will read “action to eliminate the causes of a detected nonconformity or other undesirable situation. The corrective action should eliminate the recurrence of the issue.”

A second common source of confusion and misunderstanding is deeper and more philosophical. Let’s say that company A has a situation where root cause Z is creating a potentially dangerous upward trend, but the result is still within specification. Someone can argue that because the result is still *within conformance*, the action to be taken can be categorized as preventive. Others may perfectly well argue that it is a corrective action because the cause was already acting, even though the final result is still in conformance. My opinion is that it is a preventive action, but whatever you choose is fine; the important issue is to implement the action as soon as possible.

For the sake of clarification, Table 1.1 contains the rules followed in this book.

A typical situation that occurs during nonconformance investigations is the discovery of both existing and potential root causes simultaneously. In those cases, actions taken to eliminate the causes of nonconformance will be *corrective* actions, while actions taken against identified potential causes will be considered *preventive* actions. It is perfectly possible to have both categories of actions within the same CAPA plan.

Table 1.1 Corrective or preventive?

Situation	Examples
Name it <i>corrective action</i> only if you already have a product nonconformance or process noncompliance	• Product failing specifications • Confirmed customer complaint • Use of obsolete documents • Audit finding of product nonconformance or process noncompliance
Name it <i>preventive action</i> whenever the product, process, or system is still in conformance but you discover root causes with the potential to create nonconformities	• Developing adverse trends from a monitoring system (run chart or control chart) – Shifts – Trends – High variability, and so on
Name it <i>preventive action</i> if it is purely a recommendation to enhance or improve any product, process, or system	• Changing to new material or new design • Implement new (enhanced) processes

A third controversy occurs when the same action can be considered both corrective and preventive when applied to different situations. Some CAPA professionals believe that once you have a corrective action (because you already had a nonconformance) to whatever product, process, or system you extend it, it will always be a corrective action. Other professionals, including myself, believe that if the same action can be extended to other products/processes/systems *not yet affected by this root cause*, then it should be considered a preventive action.

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2

CAPA and the Life Sciences Regulated Industry

This chapter details those requirements for the CAPA system found in several U.S. and international life science regulations, as well as in the international standard ISO 13485:2003, which apply to medical device manufacturers.

In the United States, the main sources of CAPA regulations are the current good manufacturing practice (CGMP) for finished drugs (Title 21 CFR §210 & 211) and the medical devices QSR contained in Title 21 CFR §820. Several guidelines and guidances from the FDA will be reviewed in this chapter. It is important to note that U.S. FDA regulations are generally considered to be the most comprehensive of all medical product regulations; many non-U.S. regulations are derived from FDA requirements.

In the European Union (EU), pharmaceutical goods manufacturing practices are included in volume 4 of the *EudraLex* (the rules governing medicinal products in the EU). It contains guidance for the interpretation of the principles and guidelines of CGMP for medicinal products for human and veterinary use laid down in Commission Directive 91/356/EEC, as amended by Directive 2003/94/EC and 91/412/EEC respectively. In the case of medical devices, the market is divided into three areas for regulatory purposes: (a) Active Implantable Medical Devices Directive 90/385 EEC (AIMD), (b) Medical Device Directive 93/42 EEC (MDD), and (c) In Vitro Diagnostic Directive 79/98 EC (IVDD). These three directives must be considered a set because the AIMD was amended by the MDD and the IVDD amended the MDD.

¹ FDA guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required. Author's comments: It's wise to follow the FDA current thinking.

Topics within this chapter are divided between U.S. and non-U.S. regulations. Within each, regulations are ordered by date of implementation. Following is an outline of this chapter's organization:

- FDA Pharmaceutical CGMP (Title 21 CFR §210 & 211), 1978
- FDA Medical Devices QSR (Title 21 CFR §820), 1996
- FDA Quality System Inspection Technique (QSIT), 1999
- FDA Investigation Out-of-specification (OOS) Guidance, 2006
- FDA Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations Guidance, 2006
- European Pharmaceutical GMP (*EudraLex* volume 4), 2003
- Harmonization Processes: ICH and GHTF
- ICH Q10 Pharmaceutical Quality System, 2008
- ISO 13485:2003 and the Non-U.S. Medical Devices Regulations
- Global Harmonization Task Force—Quality Management System—Medical Devices—Guidance on corrective action and preventive action and related QMS processes, 2009
- Current FDA Regulatory Trends for CAPA system

2.1 FDA PHARMACEUTICAL CGMP

The U.S. regulations governing drugs can be found in the 21 *Code of Federal Regulations*. Parts 210 and 211 are named respectively *Current manufacturing practice in manufacturing, processing, packing, or holding of drugs* and *Current manufacturing practice for finished pharmaceuticals*. Originally issued in 1971, they experienced major revisions during 1978 and 1995. Sections related to investigation of unwanted situations can be found throughout the regulations. The CAPA acronym was first adopted by the FDA during the development of the medical device quality system regulations in the 1990s.

§211.22 Responsibilities of quality control unit.

There shall be a quality control unit...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.

§211.100 Written procedures; deviations.

Written production and process control procedures shall be followed.... Any deviation from the written procedures shall be recorded and justified.

§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.

United States v Barr Laboratories, Inc. 1993

This was a landmark decision because it provided legal strength to the concept “you can’t test a product into compliance.” It also established some requirements for failure investigation additional to those already included in CGMP. Among them:

- Specifies content of failure report
- Requires listing and evaluation of lots potentially affected
- Specifies that elements of “thoroughness” vary depending on nature and impact of the event
- Establishes that all investigations must be performed promptly, within thirty business days of the problem’s occurrence, and recorded in written investigation or failure reports

2.2 FDA MEDICAL DEVICES QSR

The FDA published its *Medical Devices: Current Good Manufacturing Practice (CGMP) Final Rule: Quality System Regulations (QSR)* in October 1996 and it became effective June 1, 1997. This publication changed the focus of the regulatory agency to a “beyond compliance” approach. The various elements of the quality system (subsystems) are interconnected and interdependent. Companies must develop a systematic approach to their processes in order to be able to produce quality goods. Three main areas distinguish this new regulation from the typical GMP used for drugs:

- Design and development focus
- Purchasing control affecting suppliers, contractors, and consultants
- Corrective and preventive actions subsystem



Documents

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Three subparts of the QSR are directly related to investigation and corrective and preventive actions:

- Subpart I §820.90 Nonconforming product
- Subpart J §820.100 Corrective and Preventive Action
- Subpart M §820.198 Records (Complaint files)

§820.90(a) Control of nonconforming product establishes that:

Each manufacturer shall establish and maintain procedures to control product that does not conform to specified requirements. The procedures shall address the identification, documentation, evaluation, segregation, and disposition of nonconforming product. The evaluation of nonconformance shall include a determination of the need for an investigation and notification of the persons or organizations responsible for the nonconformance. The evaluation and any investigation shall be documented.

The CAPA subsystem is described in Subpart J §820.100:

- a. Each manufacturer shall establish and maintain procedures for implementing corrective and preventive action. The procedures shall include requirements for:
 1. 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;
 2. Investigating the cause of nonconformities relating to product, processes, and the quality system;
 3. Identifying the action(s) needed to correct and prevent recurrence of nonconforming product and other quality problems;
 4. Verifying or validating the corrective and preventive action to ensure that such action is effective and does not adversely affect the finished device;
 5. Implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems;
 6. 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

7. Submitting relevant information on identified quality problems, as well as corrective and preventive actions, for management review.
- b. All activities required under this section, and their results, shall be documented.

§820.198 describes the complaint files and establishes that:

- b. Each manufacturer shall review and evaluate all complaints to determine whether an investigation is necessary. When no investigation is made, the manufacturer shall maintain a record that includes the reason no investigation was made and the name of the individual responsible for the decision not to investigate.
- c. Any complaint involving the possible failure of a device, labeling, or packaging to meet any of its specifications shall be reviewed, evaluated, and investigated, unless such investigation has already been performed for a similar complaint and another investigation is not necessary.
- e. When an investigation is made under this section, a record of the investigation shall be maintained by the formally designated unit identified in paragraph (a) of this section. The record of investigation shall include:
 1. The name of the device;
 2. The date the complaint was received;
 3. Any device identification(s) and control number(s) used;
 4. The name, address, and phone number of the complainant;
 5. The nature and details of the complaint;
 6. The dates and results of the investigation;
 7. Any corrective action taken; and
 8. Any reply to the complainant.

2.3 FDA QUALITY SYSTEM INSPECTION TECHNIQUE (QSIT), 1999

Once the QSR were issued in 1996, the FDA created a team to re-engineer the inspection process used by the agency to perform quality system/good manufacturing practices inspections at medical device manufacturing facilities. The new inspection technique was called the Quality System Inspection Technique (QSIT). The QSIT approach to inspections was derived from the theory that there are seven sub-systems in the QSR (21 CFR, Part §820). Four primary areas were chosen to

focus the inspection: management controls, design controls, corrective and preventive actions (CAPA), and production and process controls. The remaining three subsystems are covered via “linkages” within the QSIT guide.

Satellite programs are included in the QSIT inspection due to their correlation in the inspection process with the related subsystem. The CAPA subsystem is the logical “jumping-off” point to begin inspecting for medical device reporting, corrections and removals, and medical device tacking programs that relate to a firm’s post-market activities.

Rather than check every aspect of the firm’s quality system, the so-called “top-down” subsystem approach focuses on those elements that are most important in meeting the requirements of the quality system regulation and that are key quality indicators. Between 6 and 15 inspectional objectives are provided for the review of each subsystem. The review includes both a (broad) review of whether the firm has procedures in place and appears to meet the requirements, and a closer (detailed) review of some records to verify that the requirements have been implemented in actual production, design, and daily quality assurance situations. Without a doubt, this FDA document provides more details about the CAPA system. It also represents an extraordinary benchmark, advising companies where to align internal audit programs. The QSIT describes the CAPA subsystem as one of the most important quality system elements with an equally important purpose:

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.

I strongly recommend that anyone involved in CAPA read and fully understand the ten inspectional objectives. This is the most detailed information about the CAPA subsystem the FDA ever provided:

1. *Verify that CAPA system procedures 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.

NOTE: Corrective action taken to address an existing product or quality problem should include action to correct the existing product nonconformity or quality problems and prevent² the recurrence of the problem.

The CAPA procedure should include procedures regarding how the firm will meet the requirements for all elements of the CAPA subsystem. All procedures should have been implemented. Once you have gained knowledge of the firm's corrective and preventive action procedure, begin with determining whether the firm has a system for the identification and input of quality data into the CAPA subsystem. Such data includes information regarding product and quality problems (and potential problems) that may require corrective and/or preventive action.

2. *Determine whether appropriate sources of product and quality problems have been identified. Confirm that data from these sources are analyzed to identify existing product and quality problems that may require corrective action.*

The firm should have methods and procedures to input product or quality problems into the CAPA subsystem. Product and quality problems should be analyzed to identify those that may require corrective action.

The firm should routinely analyze data regarding product and quality problems. This analysis should include data and information from all acceptance activities, complaints, service records, and returned product records. The firm must capture and analyze data from acceptance activities relating to component, in-process, and finished device testing. Information obtained subsequent to distribution should also be captured and analyzed. This 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. Examples of other sources of quality data include quality audits, installation reports, lawsuits, and so on.

3. *Determine whether sources of product and quality information that 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.*

Determine whether the firm 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, and so on), and other quality system records

² Prevent is not a good choice to define corrective action.

for unfavorable trends. Review if 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.

Determine whether the firm 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. Identification of these indicators may necessitate a vendor investigation as a preventive action. Monitoring in-process and finished device test results may reveal additional indicators of potential quality problems. For devices where stability is an issue, test results of reserve samples are continually monitored. These monitoring activities may trigger process changes, additional training activities, and other changes required to maintain the process within its tolerances and limits.

Determine whether the firm 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. Typically, SPC activities are encountered with large-volume production processes such as plastic molding and extrusion. Any continuing product improvements (in the absence of identified product problems such as nonconforming product) are also positive indicators of preventive actions.

4. *Challenge the quality data information system. Verify that the data received by the CAPA system are complete, accurate, and timely.*

Select one or two quality data sources. Determine whether the data are complete, accurate, and entered into the CAPA system in a timely manner.

5. *Verify that appropriate statistical methods are employed (where necessary) to detect recurring quality problems. Determine whether 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 non-statistical techniques. Statistical techniques include Pareto analysis, spreadsheets, and pie charts. Non-statistical 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 view of a problem and not an isolated view. For example, problems noted in service records should be compared with similar problem trends noted in complaints and acceptance information.

The full extent of a problem must be captured before the probability of occurrence, risk analysis, and the proper course of corrective or preventive action can be determined.

6. *Determine whether failure investigation procedures are followed. Determine whether the degree to which a quality problem or nonconforming product is investigated is commensurate with the significance and risk of the nonconformity. Determine whether failure investigations are conducted to determine root cause (where possible). Verify that there is control for preventing distribution of nonconforming product.*

Review the firm's CAPA procedures for conducting failure investigations. Determine whether the procedures include provisions for identifying the failure modes and determining the significance of the failure modes (using tools such as risk analysis). What is the rationale for determining whether a failure analysis should be conducted as part of the investigation, and the depth of the failure analysis?

Discuss with the firm their rationale for determining whether a corrective or preventive action is necessary for an identified trend regarding product or quality problems. The decision process may be linked to the results of a risk analysis and essential device outputs.

Using the sampling tables, select failure investigation records regarding more than one failure mode (if possible) and determine whether the firm is following its failure investigation procedures.

Confirm that all of the failure modes from your selected sample of failure investigations have been captured within data summaries such as reports, pie charts, spreadsheets, Pareto charts, and so on.

Where possible, determine whether the depth of the investigation is sufficient (root cause) to determine the action necessary to correct the problem. Select one significant failure investigation that resulted in a corrective action and determine whether the root cause had been identified so that verification or validation of the corrective action could be accomplished.

Using the sampling tables, review a number of incomplete failure investigations for potential unresolved product nonconformances and potential distribution of nonconforming product. Unresolved problems that could be of significant risk to the patient or user may require product recall if the problem cannot be resolved.

Using the sampling tables, review records regarding nonconforming product where the firm concluded corrective or preventive action was not necessary. As noted above, verify that the firm is not continuing to distribute nonconforming product. This may be an important deficiency based on the class of, and the risk associated with, the product.

Using the sampling tables, review nonconforming product and quality concessions. 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 and within the requirements of the quality system, not solely to fulfill marketing needs.

7. Determine whether appropriate actions have been taken for significant product and quality problems identified from data sources.

Where appropriate, this may include recall actions, changes in acceptance activities for components, in-process and finished devices, and so on.

Using the sampling tables, select and review significant corrective actions and determine whether the change or changes could have extended beyond the action taken. A significant action would be a product or process change to correct a reliability problem or to bring the product into conformance with product specifications. Discuss with the firm their rationale for not extending the action to include additional actions such as changes in component supplier, training, changes to acceptance activities, field action, or other applicable actions. Investigators should discuss and evaluate these issues but be careful not to say anything that could be construed as requesting a product recall.

8. Determine whether corrective and preventive actions were effective and verified or validated prior to implementation. Confirm that corrective and preventive actions do not adversely affect the finished device.

Using the selected sample of significant corrective and preventive actions, determine the effectiveness of these corrective or preventive actions. This can be accomplished by reviewing product and quality problem trend results. Determine whether there are any similar products or quality problems after the implementation of the corrective or preventive actions. Determine whether the firm has verified or validated the corrective or preventive actions to ensure that such actions are effective and do not adversely affect the finished device.

Corrective actions must be verified and (if applicable) validated. Corrective actions must include the application of design controls if appropriate.

Good engineering principles should include: establishment of a verification or validation protocol; verification of product output against documented product requirements and specifications; assurance that test instruments are maintained and calibrated; and assurance that test results are maintained, available, and readable.

9. Verify that corrective and preventive actions for product and quality problems were implemented and documented.

Using the sampling tables, select and review records of the most recent corrective or preventive actions (this sample may consist of or include records from the previously selected sample of significant corrective

actions). To determine whether corrective and preventive actions for product and quality problems and changes have been documented and implemented, it may be necessary to view actual processes, equipment, facilities, or documentation.

10. Determine whether information regarding nonconforming product and quality problems and corrective and preventive actions has been properly disseminated, including dissemination for management review.

Determine that the relevant information regarding quality problems, as well as corrective and preventive actions, has been submitted for management review. This can be accomplished by determining which records in a recent CAPA event were submitted for management review. Review the raw data submitted for management review and not the actual results of a management review.

Review the CAPA (and other procedures if necessary) and confirm that there is a mechanism to disseminate relevant CAPA information to those individuals directly responsible for assuring product quality and the prevention of quality problems.

Review information related to product and quality problems that have been disseminated to those individuals directly responsible for assuring product quality and the prevention of quality problems. Using the sample of records from objective 9 above, confirm that information related to product and quality problems is disseminated to individuals directly responsible for assuring product quality and the prevention of quality problems.

2.4 FDA GUIDANCE: INVESTIGATING OUT-OF-SPECIFICATION (OOS) TEST RESULTS FOR PHARMACEUTICAL PRODUCTION, 2006

Originally published in 1998 as draft guidance, this guidance was finally published in 2006. It derived somewhat from the previously mentioned *Barr* case. Compared to the draft version, the steps of an OOS investigation are now described more clearly. In an effort to help pharmaceutical manufacturers evaluate test results, the FDA issued a new guidance on investigating out-of-specification (OOS) results that fall outside the acceptance criteria established in drug applications, drug master files, and official compendia or by the manufacturer. The designation also covers in-process laboratory tests. The guidance document covers such topics as:

- How to investigate OOS test results
- The laboratory phase of the investigations
- Responsibilities of analyst and supervisor and other laboratory personnel

- When to expand the investigation outside the laboratory to include the production process and raw materials
- Additional testing that may be necessary
- The final evaluation of all test results

Even though this guidance applies to chemistry-based laboratory testing of drugs regulated by the Center for Drug Evaluation and Research (CDER), it's one of the few FDA documents that make clear to regulated industries the expectation and interpretation of the FDA (the "how to do" things) regarding failure investigation. What may be one of its most important parts is found within the footnote on page six, which states:

Please note that §211.192 requires a thorough investigation of any discrepancy, including documentation of conclusions and follow-up. Implicit in this requirement for investigation is the need to implement corrective and preventive actions. Corrective and preventive action is consistent with the FDA's requirements under 21 CFR part §820, Subpart J, pertaining to medical devices, as well as the 2004³ draft guidance entitled *Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations*, which, when finalized, will represent the Agency's current thinking on this topic.

In other words, the FDA's expectation is that a CAPA system similar to the one included in the medical device regulation be implemented by all regulated industry.

OOS Guidance Phase I

Whenever laboratory error is identified, the firm should determine the source of that error and take corrective action to prevent recurrence. To ensure full compliance with the CGMP regulations, the manufacturer also should maintain adequate documentation of the corrective action.

Unfortunately, most of the laboratory failures are assigned to analyst errors (for example, due to a procedure not followed) and corrected by some kind of training intervention. For an in-depth analysis of this topic, refer to items #3 and #10 of the decalogue in Chapter 5.

OOS Guidance Full Scale Investigation

When the initial assessment does not determine that a laboratory error caused the OOS result and testing results appear to be accurate, a full-scale OOS investigation using a predefined procedure should be conducted. This investigation may consist of a production process review and/or additional laboratory work. The objective of such an

³ This guidance was finally published September 2006.

investigation should be to identify the root cause of the OOS result and take appropriate corrective and preventive action. A full-scale investigation should include a review of production and sampling procedures and will often include additional laboratory testing. Such investigations should be given the highest priority. Among the elements of this phase is an evaluation of the impact of OOS results on already distributed batches.

A full-scale OOS investigation should consist of a timely, thorough, and well-documented review that includes the following information:

1. A clear statement of the reason for the investigation
2. A summary of the aspects of the manufacturing process that may have caused the problem
3. The results of a documentation review, with the assignment of actual or probable cause
4. The results of a review made to determine whether the problem has occurred previously
5. A description of corrective actions taken

If this part of the OOS investigation confirms the OOS result and is successful in identifying its root cause, the OOS investigation may be terminated and the product rejected. However, a failure investigation that extends to other batches or products that may have been associated with the specific failure must be completed (§211.192).

2.5 FDA GUIDANCE: QUALITY SYSTEMS APPROACH TO PHARMACEUTICAL CURRENT GOOD MANUFACTURING PRACTICE REGULATIONS, 2006

This guidance describes the aim of the FDA to bring the pharmaceutical GMPs to the level of the medical devices QSR. The introduction section of the guidance clearly establishes this purpose:

This guidance is intended to help manufacturers implementing modern quality systems and risk management approaches to meet the requirements of the Agency's current good manufacturing practice (CGMP) regulations (21 CFR Parts §210 and 211). The guidance describes a *comprehensive quality systems (QS) model*, highlighting the model's consistency with the regulatory requirements for manufacturing human and veterinary drugs, including biological drug products. The guidance also explains how manufacturers implementing such quality systems can be in full compliance with parts §210 and 211.

The guidance describes that 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 this guidance:

- Remedial corrections of an identified problem
- Root cause analysis with corrective action to help understand the cause of the deviation and potentially prevent recurrence of a similar problem
- Preventive action to avert recurrence of a similar potential problem

Under corrective action, the guidance establishes:

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 §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

For 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.

2.6 EUROPEAN PHARMACEUTICAL GMP (EUDRALEX VOLUME 4), 2003

EudraLex is the collection of rules and regulations governing medicinal products in the European Union. Volume 4 contains guidance for the interpretation of the principles and guidelines of good manufacturing practices for medicinal products for human and veterinary use. There are several instances within directive 2003/94/EC referring to CAPA:

Article 10: Production

1. The different production operations shall be carried out in accordance with pre-established instructions and procedures and in accordance with good manufacturing practices. Adequate and sufficient resources shall be made available for the in process controls. All process deviations and product defects shall be documented and thoroughly investigated.

Article 14: Self-inspection

The manufacturer shall conduct repeated self-inspections as part of the quality assurance system in order to monitor the implementation and respect of good manufacturing practice and to propose any necessary corrective measures. Records shall be maintained of such self inspections and any corrective action subsequently taken.

EudraLex Volume 4, Chapter 1, Quality Management, Good Manufacturing Practice for Medicinal Products (GMP) revised 2008, refers to CAPA in three areas:

Good Manufacturing Practice for Medicinal Products (GMP)

- vi. Records are made, manually and/or by recording instruments, during manufacture which demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the product was as expected. Any significant deviations are fully recorded and investigated.

Quality Control

- vi. Records are made of the results of inspections and that testing of materials, intermediate, bulk, and finished products is formally assessed against specification. Product assessment includes a review and evaluation of relevant production documentation and an assessment of deviations from specified procedures.

Product Quality Review

- iv. A review of all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventive actions taken.
- viii. A review of all quality-related returns, complaints and recalls and the investigations performed at the time.
- ix. A review of adequacy of any other previous product process or equipment corrective actions.

The manufacturer and marketing authorization holder should evaluate the results of this review, where different, and an assessment made of whether corrective and preventive action or any revalidation should be undertaken. Reasons for such corrective actions should be documented. Agreed corrective and preventive actions should be completed in a timely and effective manner. There should be management procedures for the ongoing management and review of these actions and the effectiveness of these procedures verified during self-inspection. Quality reviews may be grouped by product type (for example, solid dosage forms, liquid dosage forms, sterile products, and so on) where scientifically justified.

2.7 HARMONIZATION PROCESSES: ICH AND GHTF

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) brings together the regulatory authorities of Europe, Japan, and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration. The purpose is to make recommendations on ways to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines. The objective of such harmonization is a more economical use of human, animal, and material resources and the elimination of unnecessary delay in the global development and availability of new medicines at the same time as maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health.

The Global Harmonization Task Force (GHTF) is a voluntary group of representatives from national medical device regulatory authorities (such as the U.S. FDA) and the members of the medical device industry whose goal is the standardization of medical device regulation across the world. The representatives from its five founding members (the European Union, the United States, Canada, Japan, and Australia) are divided into three geographical areas: Europe, Asia-Pacific, and North America. Each of these actively regulates medical devices using its own unique regulatory framework. Founded in 1992, the GHTF was created in an effort to respond to the growing need for international harmonization in the regulation of medical devices.

2.8 ICH Q10: PHARMACEUTICAL QUALITY SYSTEM, 2008

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a unique project that brings together the regulatory authorities of Europe, Japan, and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product authorization. Their purpose is to make recommendations on ways to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for product authorization.

The ICH Q10 document on pharmaceutical quality systems was adopted at step 4 of the process at the ICH steering committee meeting in June 2008. At step 4 the final draft was recommended for adoption to the regulatory bodies of the European Union, Japan, and United States. It describes the CAPA system as follows:

The pharmaceutical company should have a system for implementing corrective actions and preventive actions resulting from the investigation of complaints, product rejections, non-conformances, recalls, deviations, audits, regulatory inspections and findings, and trends from process performance and product quality monitoring. A structured approach to the investigation process should be used with the objective of determining root cause. The level of effort and formality of the investigation should be commensurate with the level of risk. CAPA methodology should result in product and process improvements and enhanced product and process understanding.

2.9 ISO 13485:2003 AND NON-U.S. MEDICAL DEVICES REGULATIONS

Main non-U.S. regulations (European Community, Canada, and Japan) for medical devices are basically aligned (harmonized) with the

ISO 13485:2003 standard. ISO 13485: 2003 *Medical devices—Quality management systems—Requirements for regulatory purposes* has become the world standard for medical device quality systems and it was complemented by the publishing of ISO/TR 14969: 2004 *Medical devices—Quality management systems—Guidance on the application of ISO 13485: 2003*.

Canada has adopted ISO 13485:2003 as a Canadian national standard and labeled it CAN/CSA-ISO 13485:2003. In Europe it has been adopted as EN ISO 13485:2003. It is not mandatory to use EN ISO 13485: 2003 as the quality system standard, but any required system must be equivalent to this or better; even the low risk Class I devices benefit from a quality system that is in effect the core management system for a medical device company.

CAPA Requirements Within ISO 13485:2003

Sections 8.5 Improvement and 8.5.1 General require the organization to continuously improve the QMS. Such improvement can be implemented and maintained through the use of corrective and preventive processes, among others.

Under 8.5.2 Corrective action, the standard establishes that:

The organization shall take action to eliminate the cause of nonconformities in order to prevent recurrence. Corrective actions shall be appropriate to the effects of the nonconformities encountered. 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,
- e. Recording of the results of any investigation and of action taken, and
- f. Reviewing corrective action taken and its effectiveness.

Similarly, for 8.5.3 Preventive action:

The organization shall determine action to eliminate the causes of potential nonconformities in order to prevent their occurrence. Preventive actions shall be appropriate to the effects of the potential problems. 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, and
- d. Recording of the results of any investigations and of action taken, and reviewing preventive action taken and its effectiveness.

When comparing ISO 13485:2003 requirements with the content of the FDA QSR 21 CFR §820.100, the conclusion is that the intent of each document is consistent with the other in terms of the corrective and preventive action system. It can be concluded that the requirements established by the QSR are far more prescriptive.

Regarding control of nonconforming product, FDA's QSR provides more detail as to the items to be recorded in a nonconforming product situation. It explicitly addresses the need for an investigation in such a situation.

2.10 GHTF QUALITY MANAGEMENT SYSTEM—MEDICAL DEVICES—GUIDANCE ON CORRECTIVE ACTION AND PREVENTIVE ACTION AND RELATED QMS PROCESSES, 2009

In November 2009, the Study Group 3 of the GHTF released this proposed document for a five-month comments period. The scope of this document is to "provide guidance for establishing adequate processes for measurement, analysis, and improvement within the QMS as related to correction and/or corrective action for nonconformities or preventive action for potential nonconformities of systems, processes or products."

It also states that "the document is intended for medical device manufacturers and regulatory authorities. It is intended for educational purposes and is not intended to be used to assess or audit compliance with regulatory requirements. For this purpose the manufacturer will establish processes and define appropriate controls for measurement and analysis to identify nonconformities and potential nonconformities. The manufacturer should have established processes defining when and how corrections, corrective actions, or preventive actions should be undertaken. These actions should be commensurate with the significance or risk of the nonconformity or potential nonconformity."

Curiously, the task force decided that the acronym "CAPA" will not be used in the document because "the concept of corrective action and preventive action has been incorrectly interpreted to assume that a preventive action is required for every corrective action. This document will discuss the escalation process from different 'reactive' sources which will be corrective in nature and other "proactive" sources which will be preventive in nature. The manufacturer is required to account for both types of data sources whether they are of a corrective or preventive nature."

2.11 CURRENT FDA REGULATORY TRENDS FOR THE CAPA SYSTEM⁴

Figure 2.1 (drug and biotech products) and Figure 2.2 (medical devices) illustrate some noteworthy numbers for U.S. fiscal year 2009, which ended September 2009. Because medical devices regulation contains the CAPA subsystem, FDA statistics include CAPA as an individual item. Drug/biotech GMP does not include the term CAPA and for this reason this item cannot be individualized. However, always at the top of FDA drug inspection statistics is 21 CFR §211.192, under which most of the CAPA issues are included.

Table 2.1 (drug and biotech products) and Table 2.2 (medical devices) contain the comparison between fiscal years 2008 and 2009 for the top ten inspection observations.

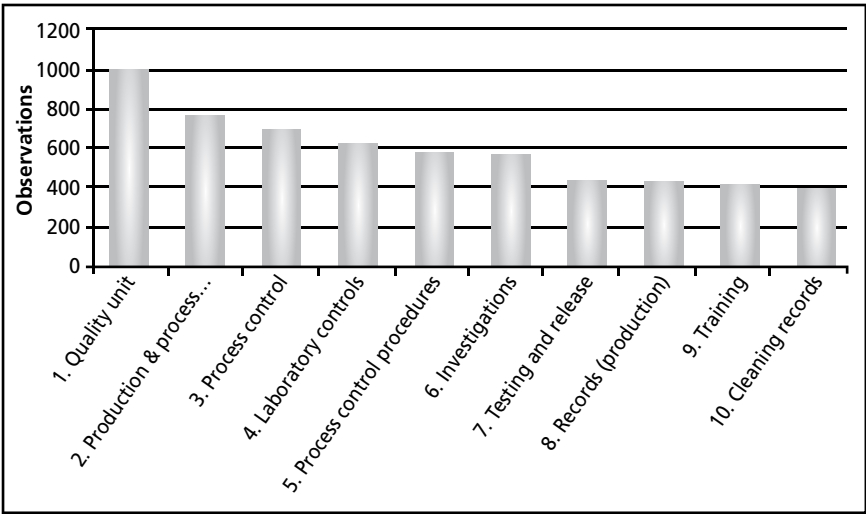


Figure 2.1 Top ten FDA observations during drug manufacturer inspections for fiscal year 2009.

⁴ Presented by FDA at the Second Regulatory Conference of the American Society for Quality Puerto Rico Section held in San Juan, Puerto Rico, on October 23, 2009.

Table 2.1 Comparison of top ten observations during drug manufacturer inspections.

Top Ten Drug/Biotech Observations Fiscal Year 2009	Top Ten Drug/Biotech Observations Fiscal Year 2008
1. Quality unit	1. Quality unit
2. Production and process control procedures	2. Process controls
3. Process control	3. Laboratory controls
4. Laboratory controls	4. Investigations
5. Process control procedures	5. Production and process control procedures (not followed)
6. Investigations	6. Cleaning and maintenance of equipment
7. Testing and release	7. Production and process control procedures (not established)
8. Records (production)	8. Training
9. Training	9. Testing and release
10. Cleaning records	10. Records (production)

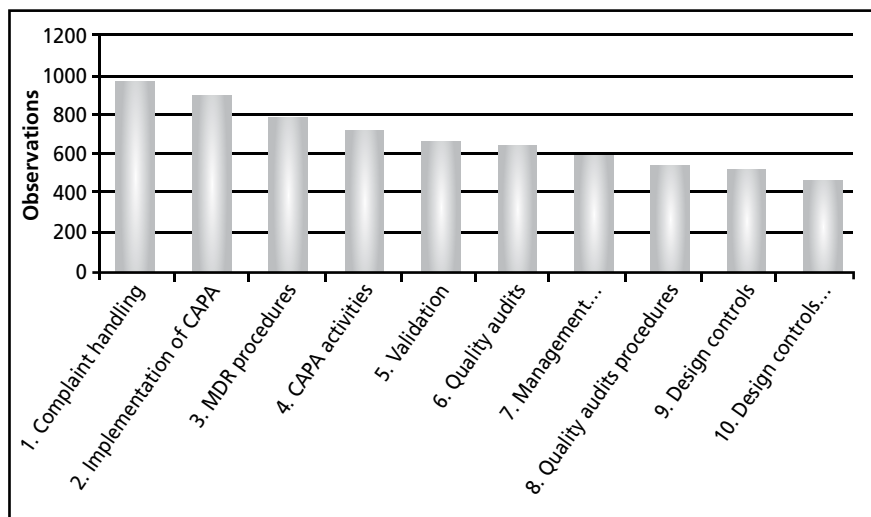


Figure 2.2 Top ten FDA observations during medical devices manufacturer inspections for fiscal year 2009.

Table 2.2 Comparison of top ten observations during medical devices manufacturer inspections.

Top Ten Medical Devices Observations Fiscal Year 2009	Top Ten Medical Devices Observations Fiscal Year 2008
1. Complaint handling	1. Complaint handling
2. Implementation of CAPA	2. CAPA procedures
3. MDR procedures	3. CAPA activities
4. CAPA activities	4. Validation
5. Validation	5. MDR procedures
6. Quality audits	6. Management responsibilities
7. Management responsibilities	7. Quality audits procedures
8. Quality audits procedures	8. Design control procedures
9. Design controls	9. Documents control procedures
10. Design controls procedures	10. Quality audits frequency

From 2002 to 2009, an average of 85 percent of medical device warning letters cited CAPA deficiencies.

3

Effective CAPA Process: From Problem Detection to Effectiveness Check

This chapter describes sequentially the entire CAPA process. It begins with problem detection, continues with root cause investigation, generation, and implementation of corrective and preventive actions, and ends with the evaluation of their effectiveness and the management of the CAPA system. Topics such as trending, training effectiveness evaluation, and risk management concepts as they related to CAPA are discussed in this chapter. Special emphasis is dedicated to the investigation of the so-called “human error.”

The basic CAPA process flow is shown in Figure 3.1 while Figure 3.2 describes the different stages and elements of the CAPA system.

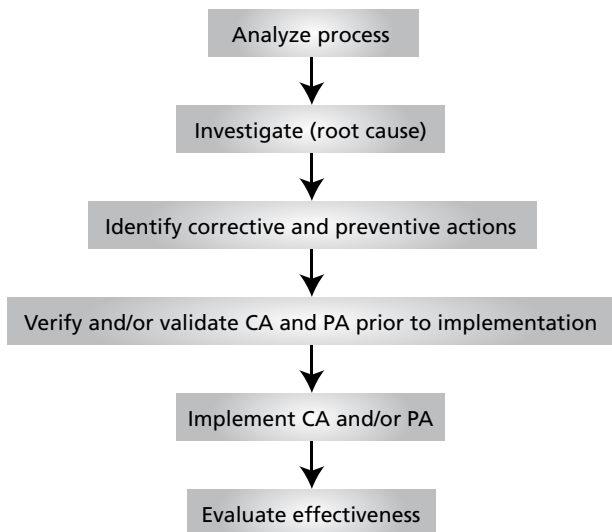


Figure 3.1 The CAPA process flow.

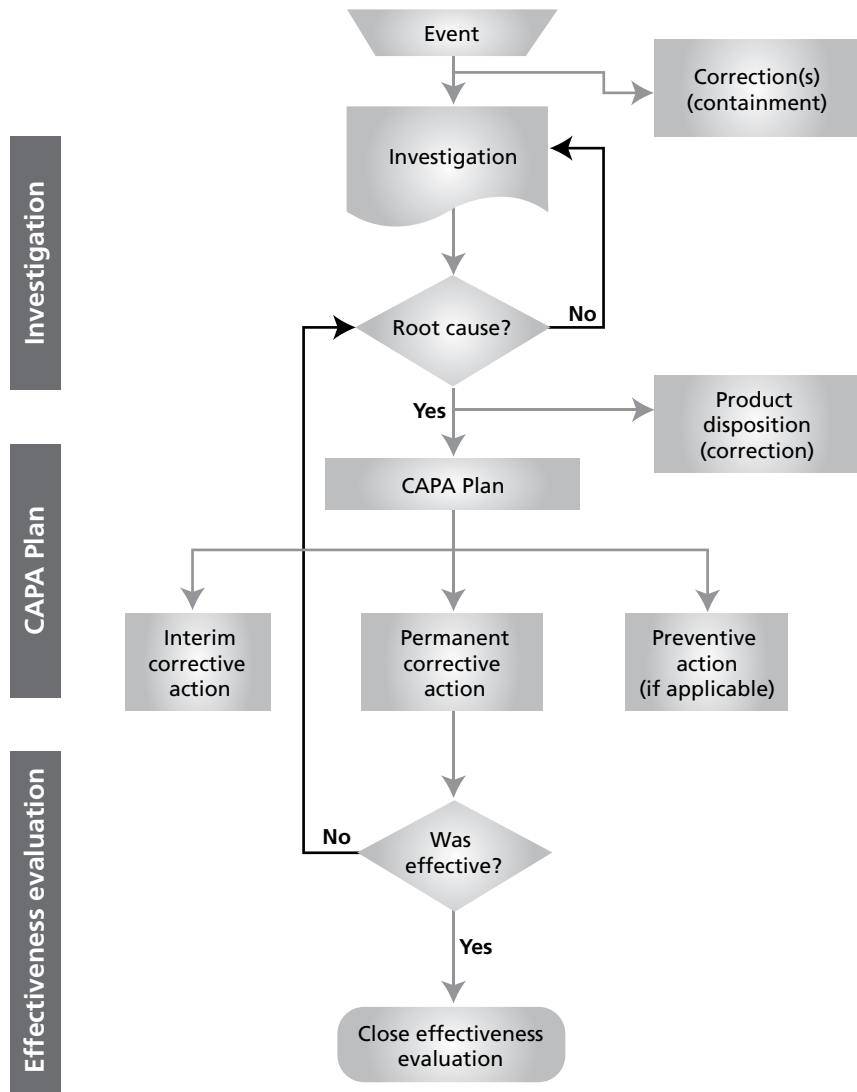


Figure 3.2 The CAPA system.

As easy as it seems, practically all manufacturers of medical regulated products are continuously struggling with their CAPA systems. The main areas of opportunity are depicted in the Figure 3.3, which represents the “vicious circle” of CAPA: lack of adequate root cause analysis leads to ineffective corrective actions, which in turn leads to recurrence of the issues, which leads to the need to investigate again and again the same old issue.

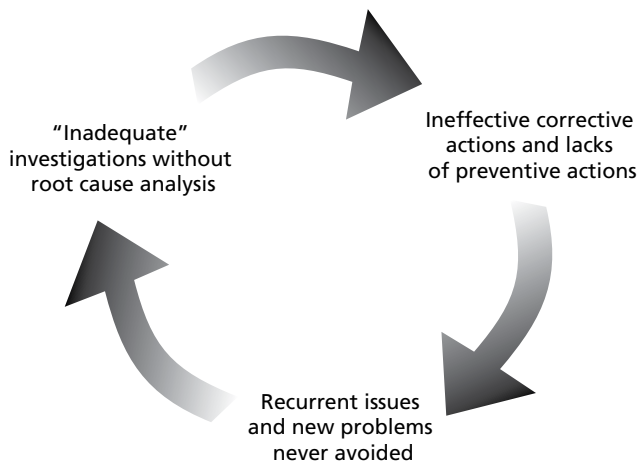


Figure 3.3 The ineffective CAPA circle.

3.1 PROBLEM DETECTION: DISCOVERING PROBLEMS

3.1.1 Source of Data About Product and Quality Issues

As previously mentioned, there is a perception in the life sciences industry that the CAPA requirements for U.S. medical devices are far more stringent than any other regulations established either by the FDA or by foreign regulators. Using this regulation as a guideline, there are three areas with requirements related to the identification of quality problems. Section 820.90(a), Control of nonconforming product, establishes that “as part of controlling nonconforming product, each manufacturer needs to evaluate each nonconformance, including a determination of the need for an investigation.”

As part of the CAPA subsystem, §820.100(a) states that “each manufacturer needs to 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.”

Finally, §820.198 (complaint files) establishes that “each manufacturer shall review and evaluate all complaints to determine whether an investigation is necessary.” This section also clarifies that any complaint involving the possible failure of a device, labeling, or packaging to meet any of its specifications shall be reviewed, evaluated, and investigated, unless such investigation has already been performed for a similar complaint and another investigation is not necessary.



Documents

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CAPA procedures must clearly identify what data sources are being used as input for the CAPA system. A frequent citation during inspections is that “the firm is not using all sources of quality data.” Among the main sources we might consider:

- Acceptance activity records relating to incoming, in-process, and finished product testing
- Stability issues
- External (customer) complaints
- Internal complaints
- FDA 483s, warning letters, and published literature
- Corrective and preventive actions
- Reports of system, process, or product nonconformities
- Process monitoring data (for example, statistical control charts, trends, run charts, yields, and so on)
- Calibration and maintenance records
- Scrap, rework, “Use As Is,” and other concessions
- Clinical adverse events
- Quality audit reports (internal, external, supplier, and third-party audits)
- Returned products analysis
- Training

In the case of medical devices, there are additional sources of quality data such as:

- Medical device reports and vigilance reports
- Installation and/or repair (servicing) reports
- Spare parts usage
- Customer and/or technical service requests
- Field service and/or warranty reports
- Customer feedback (for example, surveys)
- Historical records from previous corrections
- Lawsuits and other legal actions

3.1.2 Risk Assessment

Risk management concepts have been part of the medical devices world for many years. At first, the regulators used the term “hazard analysis” and it was part of the hazard analysis and critical control point (HACCP) methodology. For the last decade or so, HACCP terminology has been restricted to food safety and the FDA, ISO, and other regulators embraced the term “risk analysis,” which evolved to the current broader term of “risk management.” Risk analysis requirements are incorporated only into the design control (§820.30) element of FDA’s QSR, but the preamble of this regulation includes mentions about risk analysis expectations across many elements. There is also an ISO standard (ISO 14971:2007), originally issued in 2000. This establishes the risk management requirements to determine the safety of a medical device by the manufacturer during the product life cycle.

For other regulated products, such as drugs, the application of the risk management concepts is very recent. It was done in the form of an international guidance document, ICH Q9 “Quality Risk Management,” which was adopted as a non-binding guidance by the drug and biologic centers of the FDA in June 2006.

Having in mind those risk management principles, typical questions must be answered: *Do we always need an investigation? Do we always need corrective and preventive actions? How soon must companies fix their CAPA problems?*

CAPA and risk management are two interlocked concepts that cannot be separated. All of our decisions regarding CAPA must be filtered throughout the risk management system. Let’s now answer these questions.

Regarding the first question: *Do we always need an investigation?* The theoretical response is yes. Every time we detect some kind of “problem” it is necessary to look into it. Repeating the primal concept of the CAPA system, continuous improvement requires the analysis of the issue to discover its root cause before we can implement actions to prevent its recurrence. To be able to fix the cause of the problem, we must first discover its causes. Without some kind of investigation or evaluation, the probability is low that we can reach the real root causes. However, resources are not unlimited (actually they are becoming more and more scarce) and definitively, not all issues have the same significance. As the QSR preamble states, “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.” Therefore we must prioritize and risk assessment is one of the best tools we can use for this purpose. The significance of the product or quality issue can be evaluated by considering the criteria described in Table 3.1.

Table 3.1 Risk assessment criteria.

Criterion	Categories and examples
Does it have the potential for a patient or user safety issue?	• Critical or catastrophic: can cause death or significant disability to a patient or user (contaminated injectable drug, critical drug mix-up, contaminated catheter) • Marginal: can cause minor injuries to patient or user (overpotent or subpotent drugs or incorrect diagnoses) • Negligible: no injury to patient or user (cosmetic defect, empty box without product)
What is the type or classification of the product?	• Device class I • Device class II • Device class III • Intravenous drug or sterile product • Drug other than intravenous (oral, cutaneous) • Drug with narrow therapeutic ranges
Does it affect the reliability, effectiveness or usability of the product? <i>Note: consider the worst case</i>	• Totally affected: not working, not usable, or not effective (missing product, broken device) • Partially affected: underfill, low count/ quantity • Not affected
Does the issue cause the product to fall outside of established specifications?	• Final specification failure • Non-final specification failure • Acceptance specification • Validity (system suitability) specification
Does it affect the labeling of the product?	• Final label incorrect (lot number, expiration date) • Non-final label incorrect

Continued