

Handbook of
INVESTIGATION AND
EFFECTIVE
CAPA SYSTEMS

THIRD EDITION

José Rodríguez-Pérez

An illustration of a hand holding a flashlight. The hand is rendered in a stylized, flat orange color. The flashlight is dark blue with a white lens. A bright white beam of light emanates from the lens, extending diagonally across the bottom half of the cover. The background is a solid yellow-orange color.

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Handbook of Investigation and Effective CAPA Systems, Third Edition

José Rodríguez-Pérez

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Preface to the Third Edition

It has been almost 11 years since the original edition of this book was published and five since the second edition update. In this third edition, in addition to updating inspectional trending for the critical area of investigation and CAPA programs, I have revised and enhanced the case studies and the ready-to-use forms. Each chapter has been reviewed to best serve the readers of this handbook.

Chapter 1 has been improved with a new section linking investigation and CAPA programs with the overall quality culture of the company. The chapter provides information about the importance of the CAPA system within a quality system for the medical products–regulated industry. The regulatory impact of a deficient investigation and CAPA system is paramount, and it is one of the few major regulatory issues applying to all types of regulated products. Manufacturers of human drug, medical device, food, veterinary, and biologic products share the same kind of problems and opportunities for their investigation and CAPA systems.

Chapter 2 has been updated with current versions of regulations (FDA, EU, ISO 13485, and so on). It also includes up-to-date inspectional observations from the FDA and UK's MHRA. Chapter 3 includes investigation and CAPA elements of the 2015 revision of the ISO 9001 standard.

Chapter 4 covers the complete investigation and CAPA cycle, from problem detection to monitoring CAPA effectiveness, including the discussion of the tight relationship between CAPA and risk's FMEA. The barrier analysis section has been enhanced with a flowchart describing the barrier analysis process.

Chapter 5 is fully devoted to human errors and human factors and their impact in the investigation and CAPA system. It has been updated with new charts and new information related to the investigation of human errors and with new information about training and competence. The new Chapter 6 is dedicated to laboratory investigations, including a section covering the invalidation of testing results. Chapter 7 describes

a dozen of the most common pitfalls commonly encountered in the investigation and CAPA world.

Chapter 8 includes an example of an investigation and CAPA expert certification program being used by many regulated companies. It gives the elements of the certification in the form of a detailed syllabus and the elements that can be included to measure the effectiveness of the training effort. And finally, Chapter 9 contains forms and examples of the different elements (investigation report, root causes checklist, human error investigation, CAPA plan, etc.) covered in this book.

Acknowledgments

This book is dedicated to the many readers of the previous editions who shared with me their comments and praises. Your comments always made my day!

A special thanks to my friend and colleague Manuel Peña for his review and the many constructive ideas he provided for this edition.

And last but not least, a huge thanks to my wife Norma for her continuous support.

1

The Quality System and the Investigation and CAPA Element

1.1 THE QUALITY SYSTEM AND CAPA

A quality system is a set of formalized business practices that define management responsibilities for the organizational structures, 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 regarding 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 their efficiency and effectiveness. The organization must continuously improve its QMS using its quality policy, quality objectives, audit results, data analysis, corrective and preventive actions, and management review processes.

Analyzing data is an essential activity for 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 as well as data gathered from other relevant sources. The data analysis will provide information about 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 seeks to permanently eliminate 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 implementing the necessary actions to avoid a recurrence. Preventive actions are aimed at preventing the occurrence of potential problems. Corrections are the third basic element of the corrective and preventive action system (CAPA). Corrections address the symptoms rather than

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

Investigation and CAPA systems are inherently data-driven. Without adequate and 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 US companies is the existence of two separate systems (domestic and foreign) for investigating customer complaints. Another example is the lack of relationship between supplier and internal CAPA systems. By having a unified investigation and 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 problems are less readily recognized. How can a firm examine 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 for preventive actions).

An effective investigation and CAPA system must be a *closed-loop* system. This term refers to at least two elements of the system. First, it means there are sufficient controls in place to ensure the investigations and CAPA processes run 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 investigations and CAPA system. Very often, companies focus on completing the individual tasks of a particular corrective action; however, they lose track of the original purpose of the investigations and CAPA system. For example, a particular product problem may be resolved, but no evaluation is ever performed to ensure the solution was effective. In this example, the loop was never closed.

Second, an effective investigation and 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 investigation and CAPA system will require the problem to be investigated and its root causes effectively addressed with the appropriate corrective action.

A documented procedure for the investigation and CAPA system 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 action.
6. Evaluate the effectiveness of implemented 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 products 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 investigation and 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 significance and criticality, the prioritization of such actions must correlate with the risk and the magnitude of each situation.

The four key CAPA definitions are as follows:

1. **CAPA (corrective action and preventive action):** A systematic approach that includes actions needed to correct (correction), avoid recurrence (corrective action), and eliminate the cause of potential nonconforming products and other quality problems (preventive action).
2. **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.
3. **Corrective action:** Action to eliminate the causes of an *existing* (detected) nonconformity or other undesirable situation. The corrective action should eliminate the *recurrence* of the root cause(s).
4. **Preventive action:** Action to eliminate the causes of a *potential* nonconformity or other undesirable potential situation. Preventive action should prevent the *occurrence* of the potential issue by eliminating the occurrence of the root cause(s).

In summary, the purpose of the investigation and CAPA system is trifold:

- a) Collect and analyze product, process, and system information based on appropriate statistical methodology to detect existing and potential quality system problems.
- b) Investigate the cause(s) of significant (based on risk) existing and potential product and quality problems.
- c) Take appropriate, effective, and comprehensive actions.

1.2 INVESTIGATION AND CAPA RELATIONSHIP WITH OTHER QUALITY SUBSYSTEMS

The investigation and 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 an investigation and CAPA system that is compliant, effective, and efficient. All relevant subsystems that may produce nonconformances must be part of the process. The investigation and CAPA system relates to many other quality data sources within a QMS as shown in Table 1.1.

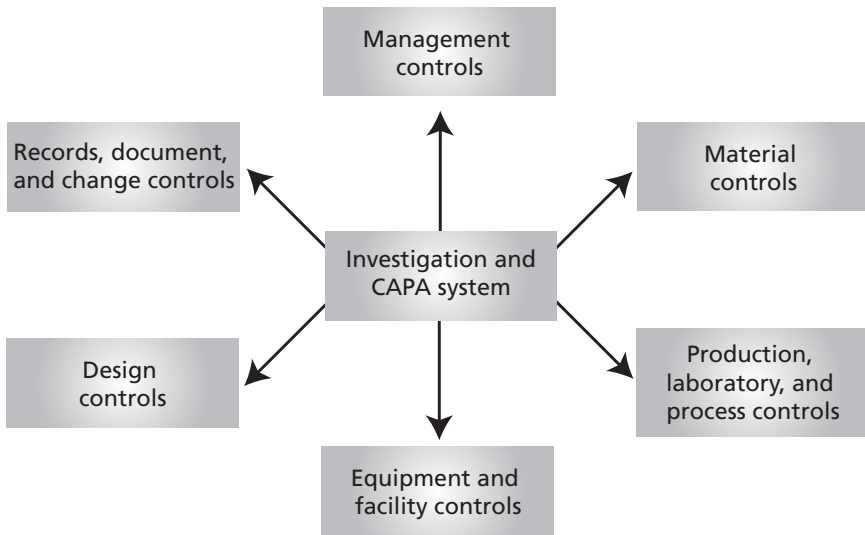


Figure 1.1 The investigation and CAPA system and the manufacturing quality system.

Table 1.1 Quality data sources within the QMS.

Quality Data Sources within the QMS
Nonconforming products
Complaints
Investigations
Process validations
Document changes
Calibration and preventive maintenance
Purchasing/supplier programs
Audits (internal, third party, regulatory inspections, etc.)
Management review
Medical device reports (MDR)
Field alert reports (FAR)
Recalls and field actions
Laboratory investigation
Design changes/product reformulations
Testing (incoming, in-process, finished product and stability)
Product returns
Service and installation

There are multiple feeders to the investigation and 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

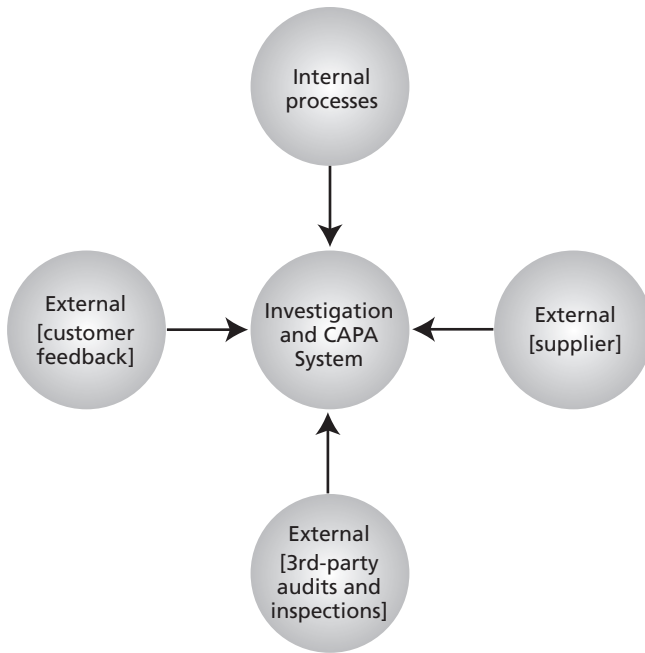


Figure 1.2 Feeders of the investigation and CAPA system.

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, as depicted in Table 1.2. A detailed discussion of those feeders can be found in Chapter 4.

Table 1.2 Investigation and CAPA sources.

Internal Sources	External Sources
Nonconforming reports Laboratory failures Equipment data (calibration, preventive maintenance, and repair) Scrap/yield data Rework data Returned product Internal audits Process control data Acceptance activities (incoming, in-process, finished product, and stability)	Complaints Field service reports Legal claims External audits FDA's MDRs FDA's FARs Scientific literature Social media

1.3 NCR OR CAPA? INVESTIGATION PHASE VERSUS FIXING CAUSES

A lot of confusion and lack of uniformity exists in many organizations when referring to what a nonconformance report (NCR) is and what should be part of a CAPA report. To complicate this even more, there is a notable lack of understanding of the meaning of CAPA within the industry. In this chapter I will try to clarify the first element, while the next chapter will delve into explaining the differences between corrective and preventive action.

The CAPA system takes care of implementing corrective and preventive actions resulting from the investigation of complaints, product rejections, nonconformances, recalls, deviations, audits, regulatory inspections and findings, and trends from process performance and product quality monitoring, as established in ICH Q10.¹

Therefore, we can clearly divide the CAPA system into the following two elements:

- 1) A structured *investigation process* approach to be used with the objective of determining the root causes. The level of effort, formality, and documentation of the investigation should be commensurate with the level of risk.
- 2) The implementation of *appropriate actions* covering
 - a. The remedial corrections of an identified problem
 - b. Corrective actions to avoid reoccurrences of the root cause(s)
 - c. Preventive actions to prevent the (first time) occurrence of the cause of a potential nonconformity or other undesirable potential situation

The investigation phase can undergo under many different names, such as complaint investigation, nonconformance investigation, deviation investigation, out-of-specification (OOS) investigation, and so on. Complaints, laboratory failures (OOS), and nonconformances are only *symptoms*, and the objective of these investigations is to understand the problem and to find the root cause(s) that creates this symptom. The investigation phase (under whatever name we may use for it) must be focused on discovering the root cause(s) associated with this event. Chapter 4 covers the investigational phase of the CAPA system extensively.

We typically refer to CAPA documents as the forms used to document actions (correction, corrective and/or preventive actions) including the CAPA plan. Chapter 4 describes this part of the CAPA system as well.

¹ ICH Q10 pharmaceutical quality system

However, there are companies that use the term *CAPA* to also identify high-level investigations. In other words, they use *CAPA* to investigate big nonconformities or high-risk situations. For this reason, one of the first things I do when I meet with managers to discuss *CAPA* is to ask them to define it.

I recommend using the investigation form to document the investigational process and use the *CAPA* form to document the action taken to fix those root causes encountered during the investigational phase.

1.4 CORRECTIVE OR PREVENTIVE?

One of the most sterile debates anyone can witness is the discussion between *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 address a root cause.

To add even more confusion, just 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. Chapter 3 discusses the use and interpretation of those concepts in the new ISO 9001:2015 standard.

A similar lack of clarity can be found in the 2006 FDA’s Guidance for Industry Quality System Approach to Pharmaceutical GMP, which adequately describes corrective action as a reactive element aimed to potentially prevent recurrence of a similar problem and describes preventive action as the action taken to avert recurrence of a similar potential problem. Table 1.3² describes the historical relation between corrective action and preventive action.

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] an *existing* (detected) nonconformity or other undesirable situation. The corrective action should eliminate the recurrence of the root cause(s).”

A second common source of confusion and misunderstanding is deeper and more philosophical. Let’s say that company A has a situation

² Modified from Arter (2015).

Table 1.3 CAPA history.

Standard	Content
1963: MIL-Q-9858A Quality program requirements	Corrective and preventive concepts placed under the same section.
1970: 10 CFR 50	Part 16 of the nuclear power generation federal regulation covered corrective action principles. No mention of preventive actions.
1987: ISO 9001—Quality management system	The first edition of the ISO 9001 standard included as clause 16 the requirement of procedures for investigating the cause of nonconforming product and corrective action needed to prevent recurrence. No explicit mention of preventive actions.
1994: ISO 9001—Quality management system	The second edition of ISO 9001 separated the concept of corrective action and preventive action.
1997: FDA 21 CFR 820	Subpart J introduced the concept of corrective and preventive action without a clear definition or separation of both concepts: “identifying the action(s) needed to correct and prevent recurrence.”
1999: FDA Quality System Inspection Technique guide	The QSIT guide defines corrective action as the “action taken to address an existing product or quality problem.” It also states that it “should include action to correct the existing product nonconformity or quality problems and to prevent the recurrence of the problem.”
2000: ISO 9001—Quality management system	Clauses 8.5.2 (corrective action) and 8.5.3 (preventive action) were maintained essentially identical to the 1994 definitions. No changes were made in the ISO 9001:2008 update.
2006: FDA’s Guidance to Industry Quality System approach to pharmaceutical cGMP regulations	In this document, the FDA tries to separate both concepts, but they didn’t select the best wording to describe preventive action: “action to avert recurrence of a similar potential problem.” Only the inclusion of “potential” helps to understand the concept of preventive.
2015: ISO 9001—Quality management system	One of the key purposes of implementing a QMS is to act as a preventive tool. As a result, the formal requirement related to preventive action was removed in the 2015 version and replaced with risk-based thinking. As a result, the corrective action clause has been replaced by a new clause named “Nonconformity and corrective action” (10.2), while the preventive action clause has been deleted and its spirit has been incorporated as part of a new clause (6.1) named “Actions to address risks and opportunities.”
2016: ISO 13485, medical devices—Quality management systems—Requirements for regulatory purposes	The current version of this international standard for medical devices is aligned to ISO 9001:2008, and therefore it maintains clauses 8.5.2 Corrective action and 8.5.3 Preventive action. See a detailed discussion of this topic under section 2.9 of this book.

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 in-conformance, the action to be taken can be categorized as preventive. Others may argue that it is a corrective action because the cause was already acting, although the final result is still in-conformance. I believe it is a preventive action, but whatever name you choose (corrective or preventive) is fine because the action is addressing a root cause, not a symptom; the important issue is to implement the action as soon as possible.

For clarification purposes, Table 1.4 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 an existing nonconformance will be corrective actions, while actions taken to eliminate identified potential causes will be considered preventive actions. It is possible to have both categories of actions within the same CAPA plan.

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,

Table 1.4 Corrective versus preventive situations.

Situation	Examples
Name it <i>corrective action</i> only if you already have a product nonconformance or process noncompliance	<ul style="list-style-type: none"> • Product failing specifications • Confirmed customer complaint • Use of obsolete or nonapproved 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	<ul style="list-style-type: none"> • Developing adverse trends from a monitoring system (run chart or control chart) <ul style="list-style-type: none"> – 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	<ul style="list-style-type: none"> • Changing to new material or new design • Implementing new (enhanced) processes

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.

Chapter 3 covers nonconformances and CAPA system requirements for the new ISO 9001:2015 with a discussion related to the elimination of the term *preventive action* from this new version.

1.5 INVESTIGATION AND CAPA INVESTIGATION RELATIONSHIP WITH QUALITY CULTURE

A strong and positive quality culture is a key component of operational excellence in the medical product industry. And more importantly, it is the road to achieve sustainable compliance in our industry. A strong, positive corporate quality culture will create manufacturing and quality product consistency, while a broken quality culture will nurture unreliable processes plagued with manufacturing and quality issues.

Having responsive deviation and investigation systems that lead to timely remediation is one of the key elements of a pharmaceutical quality culture, as presented by the FDA in 2011.³

A pharmaceutical QMS founded on a robust quality and compliance culture will provide the key elements of assurance and oversight necessary for both manufacturing and quality control laboratory processes. Using the FDA's own words:⁴

The requirements of good manufacturing practice are underpinned by a central objective: to create a system of programs, policies, processes, and facilities that prevent errors and defects. Senior managers in the drug industry are responsible for the effectiveness of this system, which is known as the Pharmaceutical Quality System (PQS). A PQS is successful when it assures an ongoing state of control. In a healthy PQS, managers establish a vigilant quality culture in which timely action is taken to prevent risks to quality. Lifecycle adaptations are made to address manufacturing weaknesses and continually improve systems. An effective process performance and product quality monitoring program provides early warning of emerging quality issues. Systemic solutions are implemented rather than ineffective shortcuts. A firm will also habitually attend to the seemingly small problems that quality experts remind us later

³ Rick Friedman, 2011, "Pharmaceutical Quality Systems: A US Perspective," <https://www.fda.gov/media/82570/download>.

⁴ FDA, 2016, "Quality Systems (Drugs)," February 22, 2016, <https://www.fda.gov/drugs/pharmaceutical-quality-resources/quality-systems-drugs>.

would accumulate into costly, complex problems. An effective PQS will ultimately support stable processes, and predictable quality and supply.

There are four areas where an overwhelming majority of pharmaceutical companies need a comprehensive overhaul to reduce their risk of lack of compliance and quality problems, as described next.

1. Investigation of deviations, OOS, OOT, and complaints

- Investigation plans are lacking.
- Timeliness for completion of investigations is lacking.
- Due dates are not realistic.
- Everything is an isolated event (lack of adequate trending).
- Root causes are not identified.
- Root causes are identified but not corrected.
- The symptom is corrected instead of the cause.
- Laboratory investigation phase II only includes review of batch record, no evaluation of product history, process capability, and so on.
- Investigation and CAPA program are not risk-based. However, the FDA does expect the manufacturer to develop procedures for assessing the risk associated to each situation, the actions that need to be taken for different levels of risk, and how to correct or prevent the problem from recurring, depending on that risk assessment.

2. Investigation of human errors

- Human factor programs are lacking.
- There is a lack of understanding why humans err.
- The human error and retraining combination is overused. Human errors cannot be eliminated nor even significantly reduced by simply telling operators to be more careful. This simplistic approach does not work because you are not addressing any root cause. Human error is more a symptom than a cause. Always ask why the human made the mistake.

3. Invalidation of OOS

- The invalidation processes is inadequate.
- Testing results including OOS/OOT are invalidated despite inconclusive, unclear root cause/objective evidence of any laboratory error (e.g., "There might be a probability that an

analyst might have performed some error inadvertently which is unidentified”).

- Retest results in invalidation.

4. Corrective and preventive action plans

- Inadequate CAPA plans are missing required elements (correction, corrective actions, preventive actions, implementation, and effectiveness verification information).
- Interim actions are lacking. The need for interim corrective actions and preventive actions is one of the most unknown and unused concepts in the regulated industry. If a corrective action cannot be implemented immediately, you must establish interim actions to avoid the recurrence of the situation while the permanent corrective action is implemented.
- True preventive actions are lacking. Most companies are in the firefighting (corrective) mode, and they lack the proactive approach that comes from the trending analysis of their in-conformance process results.
- There is lacking (or inadequate) effectiveness of the verification of the actions taken.

2

Investigation and CAPA Requirements for the Life Sciences–Regulated Industry

This chapter details the requirements for the investigation of failures and deviations to procedures and the CAPA system found in several US and international life science regulations, as well as in international standard ISO 13485, which apply to medical device manufacturers.

In the US, the main sources of investigation and CAPA regulations are the current Good Manufacturing Practices (CGMP) for Finished Drugs (Title 21 CFR §210 & 211) and the Medical Devices Quality System Requirements (QSR) contained in Title 21 CFR §820. Several guidelines and guidance¹ from the FDA will be reviewed in this chapter. It is important to note that FDA regulations are generally considered the most comprehensive of all medical product regulations; many non-US 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). This 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 now divided into two areas for regulatory purposes:

- a) The Medical Devices Regulation (Regulation [EU] 2017/745) has applied since May 26, 2021, following a four-year transition period. It repeals Directive 93/42/EEC on medical devices and the Directive 90/385/EEC on active implantable medical devices.

¹ FDA guidance documents do not establish legally enforceable responsibilities. Instead, they 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 guidance means that something is suggested or recommended, but not required. Author's comment: It is wise to follow the FDA current thinking.

- b) The In-Vitro Diagnostic Devices Regulation (Regulation [EU] 2017/746) will apply from May 26, 2022, following a five-year transition period. In the meantime, manufacturers can opt to place in-vitro diagnostic devices on the market under Directive 98/79/EC or under the new regulation if they fully comply with it.

Topics within this chapter are divided between US and non-US regulations. Within each, regulations are ordered by date of implementation. This chapter's organization is as follows:

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

2.1 FDA PHARMACEUTICAL CGMP

The US regulations governing drugs can be found in Title 21 of the 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 in 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.”

§211.160 General requirements (laboratory controls)

“Any deviation from the written specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms 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 cannot test a product into compliance.” It also established some requirements for failure investigations additional to those already included in CGMP:

- 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 30 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 CGMP used for drugs:

1. Design and development focus
2. Purchasing control affecting suppliers, contractors, and consultants
3. Corrective and preventive actions subsystem

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

1. Subpart I §820.90 Nonconforming product
2. Subpart J §820.100 Corrective and Preventive Action
3. 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 distribution and justification for concessions (allowance to use an otherwise nonconforming product, often done through a material review board) must be documented and based on scientific evidence. Concessions should be closely monitored and not become normal practice. Deficiencies would include a lack of scientific evidence for justification of the concession. If a concession resulted in a change of product specifications (form, fit, or function), the change should be evaluated for possible risk-based regulatory impact.

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.”

2.3 FDA QUALITY SYSTEM INSPECTION TECHNIQUE (QSIT)

Once the QSR was published in 1996, the FDA created a team to reengineer 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 subsystems in the QSR (21 CFR §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 tracking programs that relate to a firm's post-market activities.

Rather than evaluating 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 about 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 10 inspectional objectives. This is the most detailed information about the CAPA subsystem the FDA has 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 for 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 that corrective action taken to address an existing product or quality problem should include action to correct the existing product nonconformity or quality problems and prevent 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 include 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 after 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 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 is 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 products) 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 in 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 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 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 activity 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 them (using tools such as risk analysis). What is the rationale for determining if 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 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, verify that the firm is not continuing to distribute the 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 has 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, 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

Originally published in 1998 as draft guidance, the FDA guidance for industry *Investigating Out-of-Specification Test Results for Pharmaceutical Production* was finally published in 2006. It derived somewhat from the previously mentioned *Barr* case. The guidance document covers such topics as the following:

- 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

Although this guidance applies to chemistry-based laboratory testing of drugs regulated by the Center for Drug Evaluation and Research (CDER), it is one of the few FDA documents that make clear to regulated

industries the expectation and interpretation of the FDA (“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 this:

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 2004² 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 an investigation and CAPA system similar to the one included in the medical device regulation be implemented by all regulated industry. Chapter 6 describes the expectations and best practices for QC laboratory investigations.

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

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

² This guidance was finally published in September 2006.

system models discuss CAPA as three separate concepts, all of which are used in this guidance:

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

Under corrective action, the guidance establishes 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. 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 causes of the problem are investigated, possible actions are determined, selected actions are taken within defined timeframes, and the effectiveness of the actions taken is evaluated. It is essential to document corrective actions taken (CGMP also requires this; see §211.192).

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

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

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 investigation and CAPA systems:

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.

Chapter 1, Pharmaceutical Quality System, revised in 2013, refers to investigations and CAPA in three areas:

Pharmaceutical Quality System

- 1.4 (ix) The results of product and processes monitoring are taken into account in batch release, in the investigation of deviations, and, with a view to taking preventive action to avoid potential deviations occurring in the future.

Good Manufacturing Practice for Medicinal Products

- 1.8 (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.

- 1.8 (vii) Any significant deviations are fully recorded and investigated with the objective of determining the root cause and appropriate corrective and preventive action implemented.
- 1.8 (xi) Complaints about products are examined, the causes of quality defects investigated and appropriate measures taken in respect of the defective products and to prevent reoccurrence.

Quality Control

- 1.9 (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

- 1.10 (iv) A review of all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventive actions taken.
- 1.10 (viii) A review of all quality-related returns, complaints and recalls and the investigations performed at the time.
- 1.10 (ix) A review of adequacy of any other previous product process or equipment corrective actions.
- 1.11 The manufacturer and, where different, marketing authorization holder should evaluate the results of this review and an assessment made of whether corrective and preventive action or any revalidation should be undertaken, under the Pharmaceutical Quality System. 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, etc. where scientifically justified.

2.7 HARMONIZATION PROCESSES: ICH AND GHTF/IMDRF

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 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 efficient use of resources and the elimination of unnecessary delay in the global development and availability of new medicines while maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health.

Founded in 1992, the Global Harmonization Task Force (GHTF) was a voluntary group of representatives from national medical device regulatory authorities (the European Union, the United States, Canada, Japan, and Australia) and the members of the medical device industry whose goal was the standardization of medical device regulation across the world. The GHTF was created to respond to the growing need for international harmonization in the regulation of medical devices. In November 2012, the GHTF ceased its activities, leaving its unfinished work to the International Medical Device Regulators Forum (IMDRF), a successor organization comprised of officials from regulatory agencies—not industry—around the world. The organization had been a mainstay among the regulatory harmonization movement.

2.8 ICH Q10: PHARMACEUTICAL QUALITY SYSTEM

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 the 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 AND NON-US MEDICAL DEVICE REGULATIONS

Main non-US regulations (European Community, Canada, Australia, Brazil, and Japan) for medical devices are aligned (harmonized) with the ISO 13485:2016 standard, which has become the world standard for medical device quality systems.

Investigation and CAPA requirements within ISO 13485:2016

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

Under 8.5.2, Corrective Action, the standard establishes that:

[t]he organization shall take action to eliminate the cause of nonconformities in order to prevent recurrence. Any necessary corrective actions shall be taken without undue delay. Corrective actions shall be proportionate to the effects of the nonconformities encountered.

The organization shall document a procedure to define requirements for:

- a) reviewing nonconformities (including complaints)
- b) determining the causes of nonconformities
- c) evaluating the need for action to ensure that nonconformities do not recur
- d) planning and documenting action needed and implementing such action, including, as appropriate, updating documentation
- e) verifying that the corrective action does not adversely affect the ability to meet applicable regulatory requirements or the safety and performance of the medical device
- f) reviewing the effectiveness of corrective action taken

Records of the results of any investigation and of action taken shall be maintained.

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 proportionate to the effects of the potential problems.

The organization shall document a procedure to describe requirements for:

- a) determining potential nonconformities and their causes
- b) evaluating the need for action to prevent occurrence of nonconformities
- c) planning and documenting action needed and implementing such action, including, as appropriate, updating documentation
- d) verifying that the action does not adversely affect the ability to meet applicable regulatory requirements or the safety and performance of the medical device
- e) reviewing the effectiveness of the preventive action taken, as appropriate.

Records of the results of any investigations and of action taken shall be maintained.

When comparing ISO 13485:2016 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

The scope of the guidance on corrective and preventive action 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 would 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 COMPLAINT INVESTIGATIONS: REGULATORY EXPECTATIONS AND BEST PRACTICES

Complaint investigation is very often the beginning point of every regulatory inspection to determine whether the company has received complaints of possible (or potentially) defective products because complaints may provide leads in identifying product defects. Pharmaceutical CGMP and medical devices’ QS regulation require all complaints be reviewed, evaluated, and maintained by a formally designated unit. This unit must decide whether an investigation of the complaint needs to be performed.

Deficiencies in complaint-handling practices may result in lost complaint data essential to identifying product defects, and possibly quality system problems that have not been adequately corrected by the firm. Possible corrective actions may include recall, and/or change in the design of the device, and/or change in the manufacturing process or quality system. Inspectors will also determine if the firm has performed sufficient complaint investigation, or to the extent possible, to confirm the reported failure mode.

Each regulated company needs to evaluate complaints thoroughly to determine whether an investigation is necessary. Indicators that the company may not be complying would be shown by the following:

- A history of one or more similar failure modes that has not been investigated to confirm the reported failure mode
- No reason provided for not investigating and/or no name provided for the individual responsible for the decision not to investigate

§211.198 describes complaint files for drugs and establishes that

(a) Written procedures describing the handling of all written and oral complaints regarding a drug product shall be established and followed. Such procedures shall include provisions for review by the quality control unit, of any complaint involving the possible failure of a drug product to meet any of its specifications and, for such drug products, a determination as to the need for an investigation in accordance with 211.192. Such procedures shall include provisions for review to determine whether the complaint represents a serious and unexpected adverse drug experience which is required to be reported to the FDA in accordance with 310.305 and 514.80 of this chapter.

(b)(2) Where an investigation under 211.192 is conducted, the written record shall include the findings of the investigation and follow-up. The record or copy of the record of the investigation shall be maintained at the establishment where the investigation occurred in accordance with 211.180(c).

(b)(3) Where an investigation under 211.192 is not conducted, the written record shall include the reason that an investigation was found not to be necessary and the name of the responsible person making such a determination.

§211.198 describes complaint files for medical devices 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.

2.12 CURRENT OBSERVATIONS AND REGULATORY TRENDS FOR INVESTIGATIONS AND CAPA SYSTEMS

Investigation and CAPA systems remain two of the most frequent categories of regulatory citation in the US and elsewhere.

FDA Drug (21 CFR 211)

During fiscal year (FY) 2020 (October 2019 to September 2020), the FDA issued a total of 394 Form 483s (forms indicating areas of noncompliance at a facility) to pharmaceutical companies. A total of 1514 observations were related to finished pharmaceuticals' CGMP, with 123 of them related to the investigation and CAPA system (21 CFR 211.192). This makes inspectional observation related to investigations and CAPA the second-most frequent citation for FY 2020. There were another 23 citations for inadequate complaint investigations (21 CFR 211.198), which raises the quantity of citations for investigation and CAPA systems to 146. It is important to remember that the FDA CGMP for finished pharmaceuticals does not explicitly include a CAPA subpart of this section, and for this reason observations related to CAPA are scattered through the whole CGMP sections, as described in section 2.1.

The number of Form 483s issued during FY 2020 decreased to less than half of those issued in FY 2019. The reason is that FDA inspections came to a sudden halt with the travel and safety limitations due to the COVID-19 pandemic.

Figure 2.1 depicts the most frequent global observations during FDA inspections of drug firms for fiscal year 2020.

FDA Medical Devices (21 CFR 820)

During FY 2020, the FDA issued a total of 422 Form 483s to medical device companies. A total of 1601 observations were related to quality system regulations, with 478 of them related to the investigation and CAPA system, including complaints investigations and handling of nonconformances.

Medical device quality system regulation inspections were equally affected due to the COVID-19 pandemic.

Figure 2.2 depicts the most frequent global observations during FDA inspections of medical devices for FY 2020.

Following are some examples of recent FDA inspectional observations related to investigations and CAPA:

- Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been

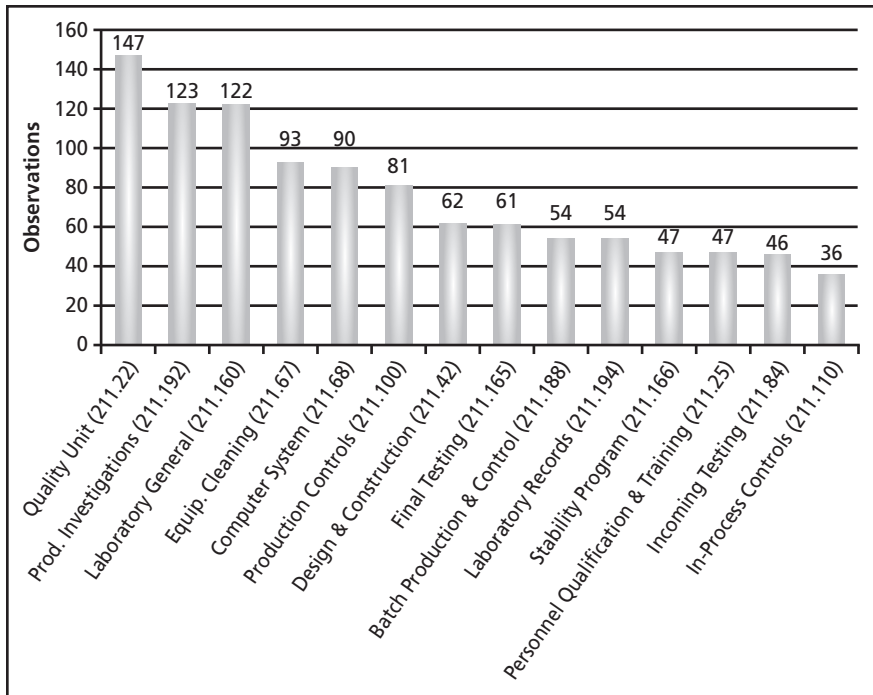


Figure 2.1 Top observations for FDA drug inspections, FY 2020.

distributed. Your firm did not adequately investigate product failures and significant defect complaints.

- You lacked thorough investigations into root causes and failed to implement prompt and effective corrective actions and preventive actions (CAPA).
- Your 18-month stability interval sample for the same lot of product x also had failing results for an unknown impurity. As part of your investigation, you re-tested your samples and obtained a new impurity OOS result at a different retention time. The retest also failed the total related compounds specification. Your investigation into this failure concluded that, because the original OOS peak was not detected in the retest, it did not confirm the original OOS result. You further determined that the impurities were not product related and were most likely due to glassware contamination.
- You failed to conduct adequate investigations into OOS test results for critical product attributes, such as an assay, for your products.

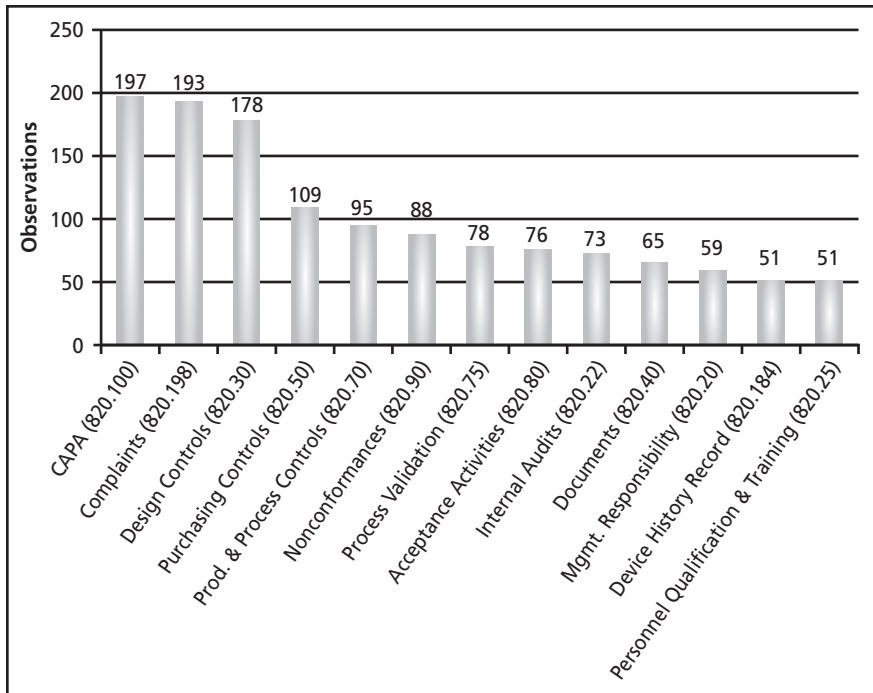


Figure 2.2 Top observations for FDA medical device inspections, FY 2020.

- Your investigations into the OOS results did not determine root causes nor include effective corrective action and preventive action (CAPA) to prevent their recurrence.
- Multiple examples of improperly invalidating initial failing OOS results were observed in your drug products. In addition, your firm has a high percentage rate (60–70%) for invalidated initial OOS test results between January 2017 and March 2019. Your response indicated your awareness of a high percentage rate of invalidated OOS test results without appropriate investigation. You stated that between January 2017 to March 2019, you had a downward trend from 77% to 41%. Major contributors are human error, instrument/column error, and method error. Your response is inadequate. You failed to provide a retrospective review of all your drug products to determine if you are attributing root cause appropriately, reporting OOS results correctly, and implementing adequate corrective and preventive actions (CAPA).
- Repeated failures at multiple sites demonstrate that executive management oversight and control over the manufacture of drugs is inadequate.

- All the complaints received since 2017 to present for sterile and nonsterile drug products have been classified as “minor.” All the QC laboratory (chemical/micro) incidents (unplanned deviations) initiated since 2018 to present have been classified as “minor.” There is a practice of invalidated failing of OOS results without scientific justification.
- Your rationales for invalidating the testing failures lacked a substantive scientific evaluation.
- Your investigations into OOS testing results were inadequate. Multiple OOS investigations were closed without assignable root cause or lacked adequate scientific justification for root cause. Despite the inadequate OOS investigations, your firm disregarded initial failing OOS results and released batches based on retested results.
- Your firm did not adequately investigate drug product failures to ensure that you did not release defective drug product.
- You lacked an adequate investigation into failing microbiological results from your purified water system.
- Your investigations into deviations and consumer complaints were inadequate. You did not adequately justify root causes, expand investigations to all potentially affected batches, implement corrective action and preventive actions (CAPA) in a timely manner, or evaluate CAPA effectiveness.
- Your firm performs corrective actions in the Product Risk Assessment (PRA) system, the Nonconformance (NCR) system, and the Equipment/Instrument Calibration (OOT) system; the corrective actions taken in these systems do not include conducting verifications of effectiveness to the specific correction to ensure the problem was resolved, recurrence was prevented, and the action did not negatively affect the finished device.
- Based on the investigation of the cause of irradiation batches receiving doses below the specified minimum dose requirement (due to incorrect packaging and product density), the firm implemented new packaging procedures and retrained employees. Irradiation batches receiving doses below the specified minimum dose requirement have recurred after implementation of the cited corrective action. The firm’s management stated that the recurring nonconformities may be attributed to employees not following directions.

Figure 2.3 is the GMP drug inspection data published by MHRA (UK’s medicines and healthcare products regulatory agency) for years

Rank	2017	2018	2019
1	1.4	1.4	C1.4 (xiv)
2	1.8	1.8	C1.8 (vii)
3	4.8	4.8	C4.8
4	4.1	4.1	C4.3
5	4.2	4.2	C1.4 (viii)
6	4.3	1.1	C4.1
7	1.1	4.3	C1.4 (xiii)
8	3.41	2.11	C4.2
9	3.19	3.19	C4 Principle
10	5.1	3.41	C1.6

Figure 2.3 Most frequent observations for MHRA drug inspections, 2017–19.

2017–19.³ Figure 2.3 depicts the top inspectional observations during those years. The investigation of anomalies is the most cited deficiency during the each of those years.

For the last three years, the top observation is related to item C1.4 (xiv):

C1.4 (xiv): An appropriate level of root cause analysis should be applied during the investigation of deviations, suspected product defects and other problems. This can be determined using Quality Risk Management principles. In cases where the true root cause(s) of the issue cannot be determined, consideration should be given to identifying the most likely root cause(s) and to addressing those. Where human error is suspected or identified as the cause, this should be justified having taken care to ensure that process, procedural or system-based errors or problems have not been overlooked, if present. Appropriate corrective actions and/or preventative actions (CAPAs) should be identified and taken in response to investigations. The effectiveness of such actions should be monitored and assessed, in line with Quality Risk Management principles.

The second most frequent observation from the last three years is related to item C1.8 (vii):

³ Medicines and Health Care Products Regulatory Agency, “2019 Deficiency Data,” https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/927085/2019_Deficiency_Data_Top_10_s.pdf.

C1.8 (vii): Any significant deviations are fully recorded, investigated with the objective of determining the root cause and appropriate corrective and preventive action implemented.

For the last year of data published (2019), another observation related to investigations and CAPA programs appears as the fifth most frequent one related to state of control (timeliness of investigations) C 1.4 (viii):

C1.4 (viii): A state of control is established and maintained by developing and using effective monitoring and control systems for process performance and product quality.

The seventh most frequent observation for the last year refers to effectiveness of the CAPA C1.4 (xiii):

C1.4 (xiii): After implementation of any change, an evaluation is undertaken to confirm the quality objectives were achieved and that there was no unintended deleterious impact on product quality.

In summary, four of the top seven observations from the last year of data published are related to the investigations and CAPA programs that truly speak to the criticality of these GMP areas. Following are some specific observations from MHRA inspections⁴:

Investigation of anomalies

- Ongoing serious deviation (related to human operational failures) had not been resolved in a robust and timely manner.
- There was no justification from the findings for the retraining of manufacturing staff. A number of the investigations appeared to place an over-reliance on retraining in the absence of a critical review of systems and supporting documentation in place at the time of the incident.
- The procedure allowed up to 60 days for the completion of the investigations categorized as critical. This was considered too long to ensure a timely review and impact assessment to be performed.
- The procedure did not detail a system for reviewing overdue investigation and an appropriate extension process.
- A large number of investigations were seen that were not closed in a timely manner or were still open a number of months beyond the stipulated expected closure time. There was no assessment of

⁴ <https://www.gov.uk/government/statistics/good-manufacturing-practice-inspection-deficiencies>

the impact of these overdue investigations and no assessment as to the root cause of the failure to follow the procedure.

- A number of investigations were seen that did not include detailed robust root cause investigation. Therefore, potential impacts were not fully assessed, and the root cause and subsequent CAPA were not robust.

CAPA

- There was a lack of a robust investigation for the reviewed compounding of complaints and nonconformances designed to identify root cause and hence appropriate actions to minimize the potential for recurrence. It was noted that the frequent use of terms such as *human error*, *isolated occurrence*, and *no trend* appeared to limit the investigation conducted.
- Root cause, implications for other batches, CAPA, and batch disposition were not clearly defined.
- The site had failed to investigate effective remedial actions in a number of areas, as evidenced by deficiencies raised at this inspection being of a similar nature to those raised at previous MHRA inspections. This indicated that the quality management system was focused on dealing with the specifics of the deficiency rather than taking a holistic view to enable the quality management system and site practices to be strengthened.

3

ISO 9001:2015: Nonconformance and CAPA Requirements

ISO 9001, the fundamental international QMS standard, has been recently revised under the new version ISO 9001:2015.¹ Changes included in the new version are so much more significant than those in the 2008 version. This standard now follows the harmonized structure (known as Annex SL) that will be followed by many other ISO standards. It requires that top management promote the use of risk-based thinking in addition to a process approach. One of the key purposes of implementing a QMS is to act as a preventive tool. As a result, the formal requirement related to preventive action (existing since the version ISO 9001:1994) was removed from this version and replaced with risk-based thinking.

The preventive action clause is no longer part of the new ISO 9001:2015 because it was associated with the corrective action clause since the ISO 9001:1994 version (see table 1.3), which is not truly an effective planning function. ISO 9001:2015 emphasizes proactive error-proofing processes to prevent problems from occurring because detection (along with root cause identification and corrective action implementation) is not as effective as it should be. Therefore, the aim of the new standard is that planning the QMS upfront is the best preventive action, making a clause tied to corrective action unnecessary.

The former corrective action clause (8.5.2 in ISO 9001:2008) has been replaced by a new clause named “Nonconformity and corrective action” (10.2) while the preventive action clause (8.5.3 in ISO 9001:2008) has been deleted and its spirit has been incorporated as part of a new clause (6.1) named “Action to address risks and opportunities.”

The 2015 version requires an organization to react to nonconformity and, as applicable, make corrections, evaluate the need for corrective action to eliminate the cause of the nonconformity, implement any action needed, review the effectiveness of the corrective action, and

¹ ISO 9001:2015 Quality management systems—Requirements.

make changes to the QMS. Clause 8.5.1 includes as a requirement the “implementation of actions to prevent human error.”

Clause 8.7, named “Control of nonconforming outputs,” includes under clause 8.7.1:

The organization shall ensure that outputs that do not conform to their requirements are identified and controlled to prevent their unintended use or delivery. The organization shall take appropriate action based on the nature of the nonconformity and its effect on the conformity of products and services. This shall also apply to nonconforming products and services detected after delivery of products, during or after the provision of services.

The organization shall deal with nonconforming outputs in one or more of the following ways:

- a) correction;
- b) segregation, containment, return or suspension of provision of products and services;
- c) informing the customer; [and/or]
- d) obtaining authorization for acceptance under concession.

Conformity to the requirements shall be verified when nonconforming outputs are corrected.

Under clause 8.7.2, the new standard establishes that “the organization shall retain documented information that:

- a) describes the nonconformity;
- b) describes the actions taken;
- c) describes any concessions obtained; [and]
- d) identifies the authority deciding the action in respect of the nonconformity.”

The spirit of the new ISO 9001:2015 is already present in concepts such as pharmaceuticals’ quality by design and medical devices’ design controls. Risk-based thinking and preventive action are key parts of the design and development processes. Moreover, the strong emphasis on risk management in this new version of the standard has already been embraced by the regulated industry with the incorporation of such concepts through guidance (pharmaceutical’s ICH Q9) and standards (ISO 14971 for medical devices or ISO 22000 for food).

Organizations rarely apply the preventive action concept at the optimal stage in a QMS because of their cost or time limitations. Preventing every potential problem and nonconformance is prohibitively expensive or even impossible.

The ISO 9001:2015 requirement of risk-based thinking can help to prevent major failures and issues, but it's unlikely that it will prevent a vast majority of potential problems. I believe that our current understanding of the preventive action concept (when correctly interpreted and applied) will survive for many years. Who can be opposed to extend any identified improvement to other products, processes, or systems not yet affected by an identified root cause(s)?

4

Effective Investigation and CAPA Processes: From Problem Detection to Effectiveness Check

This chapter describes the entire investigation and CAPA process sequentially. It begins with problem detection and associated correction or remedial actions to stop the problem; 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 investigation and CAPA system. Topics such as trending, training effectiveness evaluation, and risk management concepts as they relate to investigation and CAPA are discussed in this chapter. Special emphasis is devoted to the investigation of the so-called “human error.”

The basic investigation and CAPA process flow is shown in Figure 4.1, while Figure 4.2 describes the different stages and elements of the investigation and CAPA system.

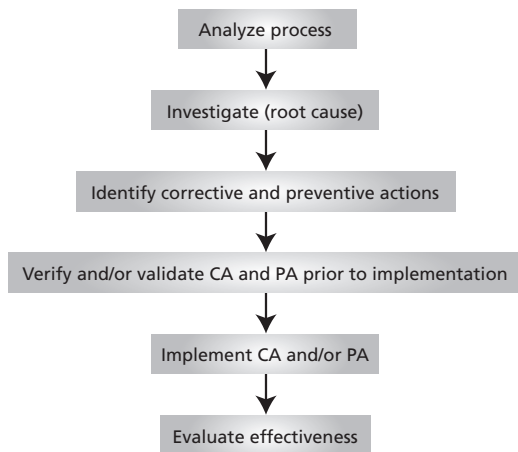


Figure 4.1 The investigation and CAPA process flow.

As can be seen in Figure 4.2, the entire system is made up of three phases: investigation phase, CAPA plan phase, and effectiveness evaluation phase. One of the major mistakes I have seen is the use of words such as *analyze*, *evaluate*, *assess*, and so on, as actions of the CAPA plan phase. None of these actions belong to the CAPA plan phase. In fact, they are part of the extension of the investigation. So, they really belong to the investigation phase, not to the CAPA plan phase.

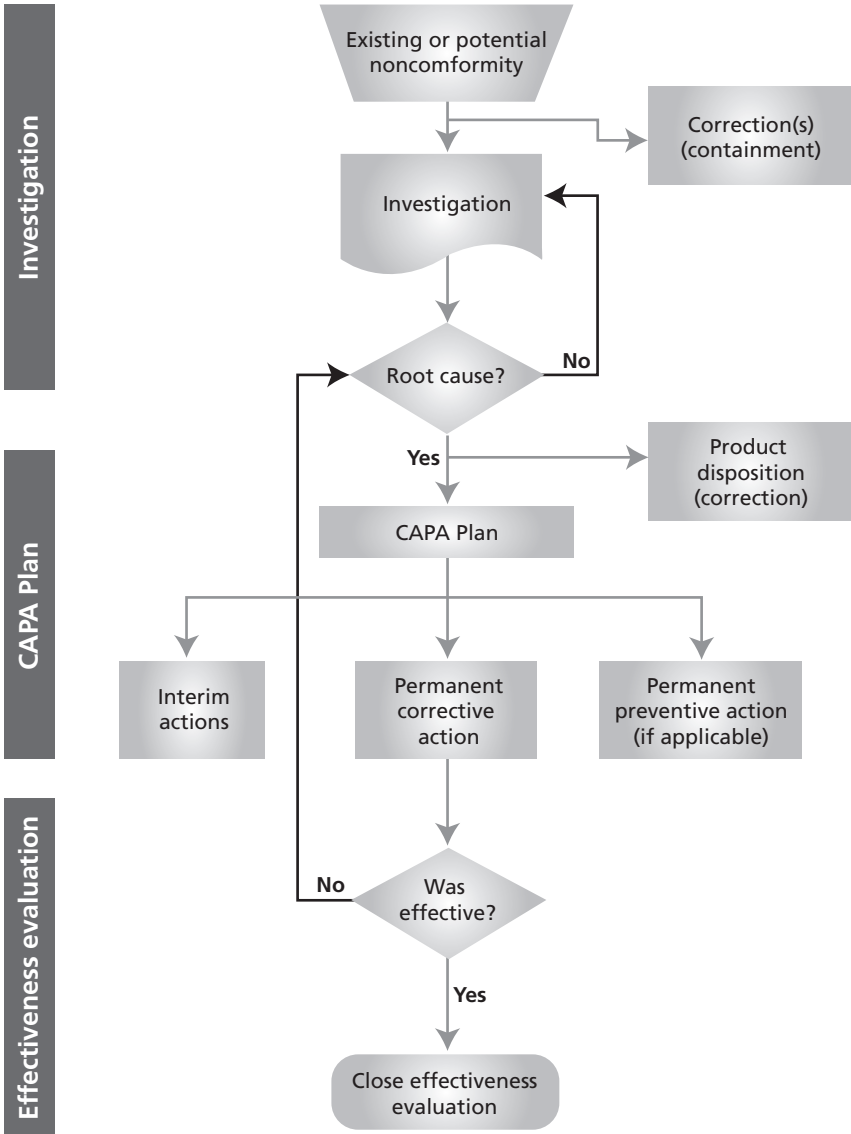


Figure 4.2 The investigation and CAPA system.

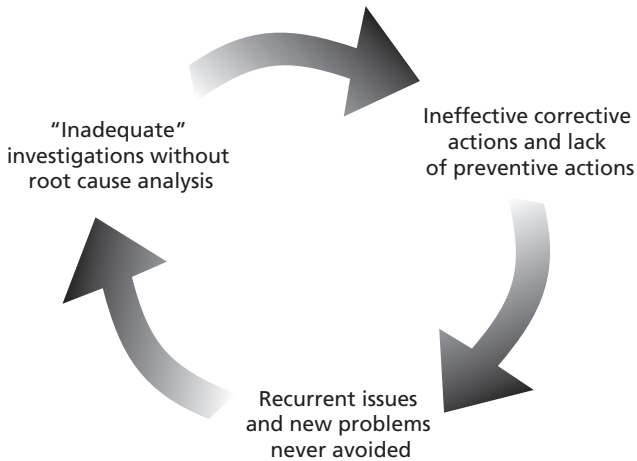


Figure 4.3 The ineffective investigation and CAPA circle.

As easy as it seems, practically all manufacturers of medically regulated products are continuously struggling with their investigation and CAPA systems. The main areas of opportunity are depicted in the Figure 4.3, which represents the “vicious circle” of investigation and 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 the same old issue again and again.

4.1 PROBLEM DETECTION: DISCOVERING PROBLEMS

4.1.1 Sources of Data about Product and Quality Issues

As previously mentioned, there is a perception in the life sciences industry that the investigation and CAPA requirements for US medical devices are far more stringent than any other regulations established either by the FDA or by foreign regulators. With this regulation as a guide, 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 analyze 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.

These three sections are inter-related; that is, they cannot be interpreted alone. Section §820.90(a) establishes that all nonconformities shall be evaluated in order to determine if an investigation is needed. Meanwhile, §820.198 establishes that all complaints shall be evaluated to determine whether an investigation is needed. However, §820.198 goes further to require the name of the person responsible and the rationale when an investigation is not performed. Therefore, both sections provide a pathway to open an investigation (including a root cause analysis, corrective and preventive actions, and effectiveness evaluation) or just simply implement corrections and trend monitoring. Figure 4.4 shows the inter-relationship of §820.90, §820.100, and §820.198.

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 are the following:

- Acceptance activity records relating to incoming, in-process, and finished product testing
- Stability issues
- External (customer) complaints
- Internal complaints

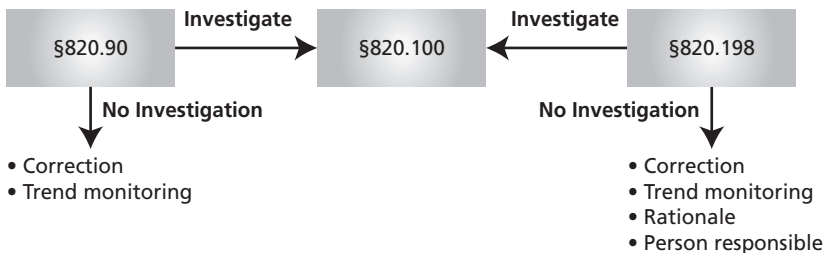


Figure 4.4 Relationship among §820.90, §820.100, and §820.198.

- FDA 483s, warning letters, and published literature
- Corrective and preventive actions
- Reports of system, process, or product nonconformities
- Process monitoring data (e.g., statistical control charts, trends, run charts, yields, etc.)
- Calibration and maintenance records
- Scrap, rework, “use as is,” and other concessions
- Clinically adverse events
- Quality audit reports (internal, external, supplier, and third-party audits)
- Returned products analysis
- Training

There are additional sources of quality data:

- Field alert reports, 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 (e.g., surveys)
- Historical records from previous corrections
- Lawsuits and other legal actions

4.1.2 Initial Impact Assessment

A preliminary evaluation of the impact of the event based on the initial data and evidence available is one of the first actions to be taken once a problem is detected. It’s important to establish, as soon as possible, the boundaries of the problem. If confidence exists that no other material has been affected, it must be supported with objective evidence. We need to consider product (lots/batches) directly affected by the event as well as any other product potentially affected. Special attention must be placed on products that ran before and after the lot under investigation. One of the most critical questions at this point is to establish whether any material affected by this situation reached the customer.

The preliminary investigation must determine whether any affected materials (in-process product, purchased or manufactured raw materials, or packaging components) have been processed beyond the area in which

the situation was identified. If so, these other areas must be included, as appropriate, in the impact assessment.

Until the most probable root causes can be established, *everything is suspicious*. For example, once a product fails a specification

- Other batches manufactured with the same components could be affected
- Other batches manufactured / tested with the same equipment could be affected
- Other batches manufactured / tested by the same operator / analyst could be affected

Once the root cause is determined (e.g., a component caused the failure), we can establish that

- Other batches manufactured with the same components could be affected
- Other batches manufactured / tested with the same equipment were not affected
- Other batches manufactured / tested by the same operator / analyst were not affected

The requirements for this impact assessment are clearly established in the CGMP (21 CFR §211.192):

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.

In the landmark judicial decision *United States v. Barr Laboratories, Inc.* (1993), there are requirements for listing and evaluating lots potentially affected by the failure under investigation. As a third example, the 2006 FDA guidance on out-of-specification investigations establishes that

Once the OOS is confirmed, the investigation changes from an OOS investigation into a batch failure investigation, which must be extended to other batches or products that may have been associated with the specific failure (§211.192).

4.1.2.1 Risk Assessment

Risk management concepts have been part of the medical devices' world for many years.¹ At first, the regulators used the term *hazard analysis*, and

¹ For an in-depth review of this topic, see Rodríguez-Pérez (2017).

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. Thus, 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 14971:2019), originally issued in 2000 and first revised in 2007. 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 nonbinding 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 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 investigate it. Repeating the primal concept of the investigation and 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 investigation or evaluation, the probability that we can reach the real root causes is low. However, resources are not unlimited (they are becoming more and more scarce), and definitively not all issues have the same significance. As the QSR preamble states, "[A]t 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 4.1.

Most regulated companies perform risk evaluation based on the frequency and the severity (importance, significance) of the event. Situations in which the frequency is rare and the severity is low may not require further investigation. Nevertheless, this evaluation must be documented. In other words, if you can demonstrate (with objective

Table 4.1 Risk assessment criteria.

Criterion	Categories and Examples
Does it have the potential for a patient or user safety issue?	<ul style="list-style-type: none"> • 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 (over- or subpotent drugs, or incorrect diagnoses) • Negligible: No injury to patient or user (cosmetic defect, empty box without product)
Type or classification of the product	<ul style="list-style-type: none"> • Device class I/II • Device class III • Intravenous drug or sterile product • Drug other than intravenous (oral, cutaneous) • Drug with narrow therapeutic ranges • Over-the-counter product
Does it affect the reliability, effectiveness, or usability of the product? Note: Consider the worst case.	<ul style="list-style-type: none"> • 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?	<ul style="list-style-type: none"> • Final specification failure • Non-final specification failure • Acceptance specification • Validity (system suitability) specification
Does it affect the labeling of the product?	<ul style="list-style-type: none"> • Final label incorrect (lot number, expiration date) • Non-final label incorrect
How frequent is the problem?	<ul style="list-style-type: none"> • First-time occurrence • Occasional • Frequent
Does the frequency of the occurrence of the issue change?	<ul style="list-style-type: none"> • Improving • Worsening
How difficult is to detect the issue?	<ul style="list-style-type: none"> • Not detectable (customer detected it) • Detected by chance (shipping operator detected it) • Detected by process (inspection detected the failure)
Does it represent a regulatory risk (can this product be considered as adulterated or misbranded)?	<ul style="list-style-type: none"> • Mix-ups • Product released prior to completion of its record review

Note: Drugs also include biopharmaceutical products.

evidence) that the problem has low frequency and no significant danger, then you could pass on this investigation and focus your effort on more significant issues.

The biggest concern with this evaluation is that a vast majority of regulated companies focused the severity evaluation exclusively on the safety of the patient. Based on that evaluation, they assigned very low risk scores to deviations and nonconformances that represent major violations of CGMPs and therefore render such products adulterated.

Do we always need corrective and preventive actions? If you investigated and discovered the root causes of the problem, it would be insane not to fix them. The FDA position in this matter can be found in the preamble to the October 7, 1996, Medical Devices QSR. In comment 159 of the preamble, which relates to the degree of corrective or preventive actions, the FDA states that the “FDA cannot dictate in a regulation the degree of action that should be taken because each circumstance will be different, but FDA does expect the manufacturer to develop procedures for assessing the risk, the actions that need to be taken for different levels of risk, and how to correct or prevent the problem from recurring, depending on that risk assessment.”

A remarkable observation on this side of the investigation and CAPA system is that many companies always require both corrective and preventive actions even in situations where no preventive action can be applied. In some cases, the reason to require them is simply that the CAPA form includes both types of actions and therefore both are always required.

How soon must companies fix their CAPA problems? The third question refers to the timeliness of failure investigations and corrective or preventive actions. Time frames for completing the different CAPA actions must be established based on the risk of the situation under investigation. In Chapter 6, I will elaborate on this issue because it constitutes one of the biggest opportunities for improving CAPA systems. One simple approach used by several companies is to complete investigations (the root cause investigation) in four weeks for low-risk situations, three weeks for medium-risk situations, and two weeks for high-risk situations. In the cases previously mentioned, risk classification is normally based on frequency and severity alone.

Our recommendation is to use risk management criteria to determine how deeply and how fast every nonconformance or deviation should be treated. These risk criteria must be clearly defined in written procedures. One example might be establishing who is responsible for evaluating product or quality issues and determining whether a failure investigation is necessary. Another example would be maintaining a record when no failure investigation is made, including the reason and the name of the individual responsible for the decision. The procedure should also

determine the depth to which a failure investigation is to be carried out and when an investigation should not pursue corrective action.

Table 4.2 depicts a simple way to carry out this task by segregating nonconformances and deviations into three categories based on the previously described risk criteria. For each situation, an overall risk score is determined by considering the worst-case scenario of the eight dimensions under analysis. Check marks indicate the risk classification that is assigned to each dimension. For example, if the problem can have a critical or catastrophic impact on the safety of the patient, then its risk score must be high independent of any other dimension such as product classification, problem detectability, and so on.

Table 4.2 can be applied to processes and systems, including equipment failure, where no product was directly affected.

Table 4.2 Risk assessment score matrix.

Criterion	Categories	Risk Score		
		Negligible or Low (1)	Medium (2)	High (3)
Safety	Critical or catastrophic			✓
	Marginal		✓	
	Negligible	✓		
Product classification	Device class I or II	✓		
	Device class III		✓	
	Intravenous drug or sterile product		✓	
	Drug with narrow therapeutic ranges		✓	
	Other drug products or OTC drugs	✓		
Reliability or effectiveness	Totally affected			✓
	Partially affected		✓	
	Not affected	✓		
Product specification	Final specification failure			✓
	Non-final specification failure			
	Specifications are not affected			

(Continued)

(Continued)

Table 4.2 Risk assessment score matrix.

Criterion	Categories	Risk Score		
		Negligible or Low (1)	Medium (2)	High (3)
Product labeling	Final product labels			✓
	Non-final product labels			
	No labeling is affected	✓		
Frequency or trending	First-time occurrence (isolated event)	✓		
	Occasional but improving			
	Occasional but worsening		✓	
	Frequent		✓	
Detectability	Not detectable or not detected			✓
	Detected by chance			
	Detected by the regular process	✓		
Regulatory risk	Product can be considered adulterated or misbranded			✓
	Product is not adulterated nor misbranded	✓		

Note: Drugs also include biopharmaceutical products.

Table 4.3 is an example of how to use this risk assessment score matrix for an issue affecting a class III medical device.

Table 4.3 Example of risk assessment.

Criterion	Categories	Risk Score		
		Negligible or Low (1)	Medium (2)	High (3)
Safety	Critical or catastrophic			✓
	Marginal		✓	
	Negligible	⊗		

(Continued)

(Continued)

Table 4.3 Example of risk assessment.

Product classification	Device class I or II	✓		
	Device class III		⊗	
	Intravenous drug or sterile product		✓	
	Drug with narrow therapeutic ranges		✓	
	Other drug products or OTC drugs	✓		
Reliability or effectiveness	Totally affected			✓
	Partially affected		✓	
	Not affected	⊗		
Product specification	Final specification failure			✓
	Non-final specification failure			
	Specifications are not affected	⊗		
Product labeling	Final product labels			✓
	Non-final product labels			
	No labeling is affected	⊗		
Frequency or trending	First-time occurrence (isolated event)	⊗		
	Occasional but improving	✓		
	Occasional but worsening			
	Frequent		✓	
Detectability	Not detectable or not detected			✓
	Detected by chance		✓	
	Detected by the regular process	⊗		
Regulatory risk	Product can be considered adulterated or misbranded			✓
	Product is not adulterated nor misbranded	⊗		

A medium risk score was determined for the example used. Now we can use this risk score to determine the content and priority level of each nonconformance investigation, as detailed in Figure 4.5. Table 4.4 describes the characteristics of each nonconformance investigation type.

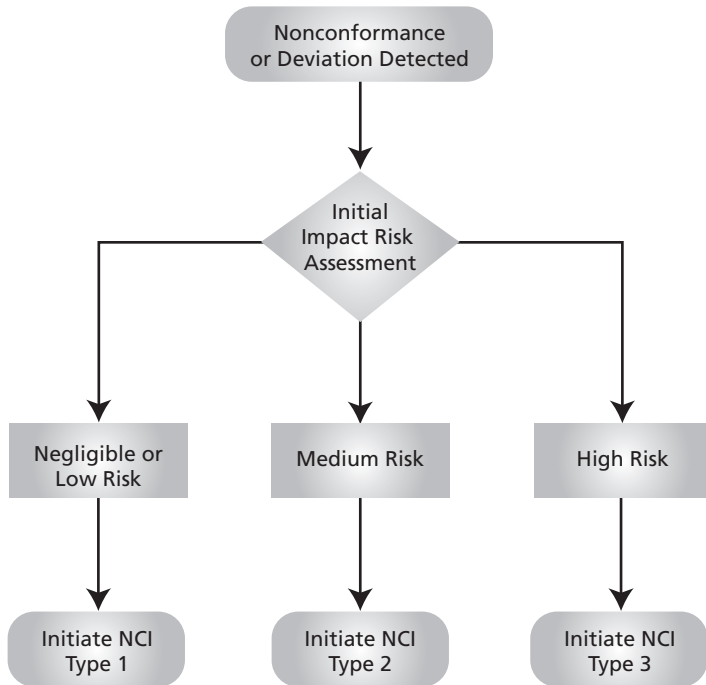


Figure 4.5 Risk prioritization of investigations.

4.1.3 Process Trending

Process monitoring is a critical element of continuous improvement. Detection of nonconformances (e.g., the failure of a specification) is not an issue in the life sciences–regulated industry, and most of the time failure triggers an investigation within the CAPA system. The problem is the lack of monitoring for in-conformance processes. This is the kind of data that can allow us to identify potential causes of a nonconforming product or other quality problems. Many regulated companies are used to monitoring environmental data, but they do not extend these concepts into the manufacturing or quality control test data. Without process monitoring, the control state expected from a quality management system cannot be achieved.

Table 4.4 Types of nonconformance investigations.

Nonconformance Investigation (NCI)		
Type 1	Type 2	Type 3
<ul style="list-style-type: none"> • Only negligible or low-risk scores are obtained • 3 days to complete • Document the event and the correction(s) taken • Monthly tracking and trending of type 1 NCI 	<ul style="list-style-type: none"> • At least one dimension had a medium-risk score • 30 days to complete • Document the event, root cause analysis, and the correction(s) taken • Need to generate a CAPA plan 	<ul style="list-style-type: none"> • At least one dimension had a high-risk score • 20 days to complete • Document the event, root cause analysis, and the correction(s) taken • Need to generate a CAPA plan

Note: Complete nonconformance investigation means document approval.

FDA regulations and guidance contain plenty of requirements and recommendations regarding the trending of processes. For medical devices, QSR establishes, on §820.100, the following:

- 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.

For pharmaceutical manufacturing, the 2004 FDA Sterile Product Guidance states that “the QCU [Quality Control Unit] should provide routine oversight of near-term and long-term trends in environmental and personnel monitoring data.” More recently, the landmark 2006 FDA Guidance for Industry Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations devoted a whole section to the topic titled “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 this 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 the CGMP pharmaceutical regulations [§211.180(e)] require 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.

Trending relates to process behavior or process stability; process capability relates to the ability of the process to meet the customer specification. Process monitoring reveals the voice of the process. Statistical tools appropriate for this task include run charts, control charts, scatter diagrams, and regression analysis. However, it is important to remark that trending should not be confused with statistical significance. The use of appropriate terminology and wording helps in this task. When we obtain an out-of-specification (OOS) task, we call it a failure; however, when we obtain an out-of-trend (OOT) task, we call it an excursion.

Each company must develop a process monitoring/trending procedure where it must define what an adverse trend is. When an adverse trend is identified, an investigation should be initiated to identify the root cause(s) to implement effective corrective and preventive actions.

For environmental monitoring, both short- and long-term trending are used. At least three years of historical data must be kept for the purpose of long-term trending.

Short-term trending:

- Identifies potential drifts from historical results
- Amount required should be based on risk assessment of potential impact on manufactured products
- Provides daily and weekly excursion trend analysis
- Uses single-sample point plots of all critical surfaces, areas, or utilities

Long-term trending:

- Documents the state of control of environmental conditions; establishes normal (“natural”) variability

- Helps to evaluate the effectiveness of training, performance, cleaning methods, maintenance procedures, CAPA, and so on
- Is used for weekly and monthly excursion trend analysis

The basic question when analyzing data for process trending purposes is this: *Do you see any trend or pattern that deserves further investigation?*

Several common mistakes occur during trending analysis:

- We conclude that there is a trend when what we are “detecting” is the common variation present in all processes.
- We are unable to detect a real trend or pattern (we’re trend blind, a common problem in the regulated industry).
- We fail to evaluate enough data points to cover normal variation of the process under analysis. (At least 15–20 are required.)

Verify whether the most recent data points are within the expected range of variation. Do you see any pattern? Any daily, weekly, monthly, or seasonal trend? Are SPC or control charts the correct tool for process trending?

Most of the processes in the life sciences–regulated industries are not stable over long periods of time. For example, the critical quality attributes of a drug are most likely determined by the incoming materials used during manufacturing. As soon as we change the raw material, we can observe dramatic changes in the results of quality control tests. For this reason, typical control charts are not the best option to monitor those processes. A good substitute is the run chart, which is basically a control chart without limits:

- Both have the same purpose: to distinguish common from special-cause variation in the data produced by a process.
- Run charts originated from control charts.
- Run charts evolved from the development of these control charts, but run charts focus more on time patterns while control charts focus more on acceptable limits of the process.
- Run charts are simple to construct and to analyze and can be used with any process and any type of data.

Nonconformance investigations type 1 (see Table 4.4) must be evaluated periodically using a Pareto chart to focus on the most prevalent issues. Other available tools such as run charts or control charts are recommended to monitor the performance of the most significant processes and activities such as rework.

I do recommend a monthly review of the investigation and CAPA system trends. If, for some reason, this schedule is not feasible, review it bimonthly or quarterly. Less often than quarterly is not recommended.

Figure 4.6 is an example of monitoring the scrap rate of a process. Baseline ranges from 2% to 3%, but something happened during December and the scrap rate rose to 7%. An investigation seems appropriate.

The book *Process Monitoring and Improvement Handbook* is an excellent reference for this topic of trending.²

4.2 PROBLEM INVESTIGATION: DISCOVERING ROOT CAUSES

Many investigation reports conclude that the root cause was *human error* or procedures not followed (by some human being) and immediately jump to solutions such as retraining. Most of the time these “solutions” are ineffective because they missed the principal and key element of the investigation and CAPA system: root causes.

Problems are best solved by identifying and eliminating root causes, as opposed to merely addressing the immediately obvious symptoms. By directing corrective actions at root causes, we hope that the probability of problem recurrence will be minimized. Root cause analysis is one of the most widely used approaches to problem solving, and it is considered an iterative process, part of the continuous improvement tool collection.

Many times, the problems are consequences of a combination of causes or, even worse, of the interaction of these causes. For this reason, a systematic approach to root cause analysis and problem solving is

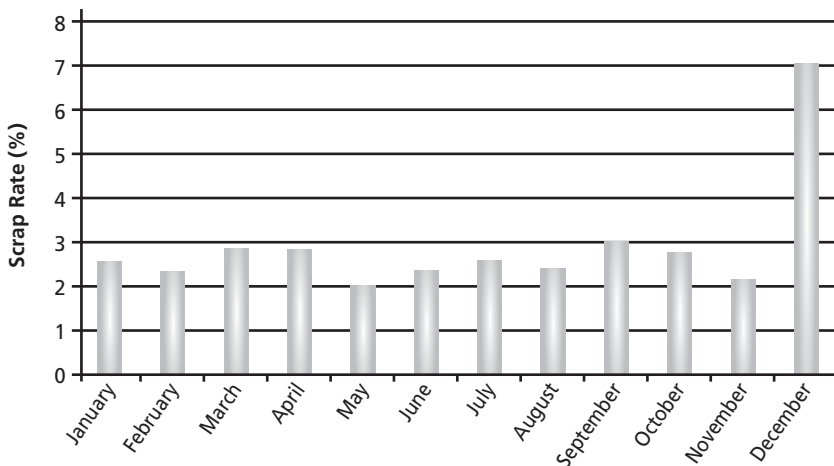


Figure 4.6 Scrap monthly rates.

² See Pena-Rodríguez (2018).

9.7 FINAL RECOMMENDATIONS

Table 9.11 Final investigations and CAPA recommendations.

Topics	Recommendations
Problem detection	<ul style="list-style-type: none"> • Use risk assessment criteria to prioritize your investigation and CAPA activities • Monitor in-conformance results • Consider all available sources of CAPA data
Problem investigation	<ul style="list-style-type: none"> • Do not use human error as root cause • Establish the requirements for using problem-solving tools (comparison diagram, timeline, fishbone, FTA, etc.).
Human error investigation	<ul style="list-style-type: none"> • Interview human beings involved with each incident • Investigate human factors • Look for precursor (latent) factors
CAPA plan	<ul style="list-style-type: none"> • Give at least one corrective action per each root cause • Do not use <i>evaluate</i>, <i>analyze</i>, or <i>assess</i> as corrective or preventive actions • Do not overuse retraining • Use realistic due dates
Effectiveness evaluation	<ul style="list-style-type: none"> • Do not use a fixed period • Link it to root cause, not symptoms
Management of the CAPA system	<ul style="list-style-type: none"> • Maintain only one CAPA system • Correlate systems, if using more than one (external, internal, etc.) • Develop your investigation/CAPA personnel
Documenting investigations/ CAPA	<ul style="list-style-type: none"> • Clarity • Readability • Economy • Correctness
Training for investigations/ CAPA	<ul style="list-style-type: none"> • Certify your investigation and CAPA personnel • Evaluate the effectiveness of your investigation and CAPA training

(Continued)

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Table 9.11 Final investigations and CAPA recommendations.

Human error prevention	<ul style="list-style-type: none">• Eliminate the error source; make the error impossible by design• Do not allow personnel to operate by memory (read, execute, and document is the best recipe to prevent human errors)• Reduce the error opportunity using physical barriers• Mitigate the consequences of an error• Make the errors detectable before they create a greater problem• Reinforce supervision for new employees, tasks, or equipment• Improve documents/work instructions• Employees without supervision must follow the procedures• Provide reminders (warnings) when appropriate• Improve the effectiveness of the training
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Appendix A

ADDITIONAL RESOURCES

- Andersen, Bjørn, and Tom Fagerhaug. 2006. *Root Cause Analysis: Simplified Tools and Techniques*. 2nd ed. Milwaukee, WI: ASQ Quality Press.
- Gawande, Atul. 2010. *The Checklist Manifesto: How to Get Things Right*. New York: Metropolitan Books.
- Phillips, Jack, and Ron Stone. 2002. *How to Measure Training Results: A Practical Guide to Tracking the Six Key Indicators*. New York: McGraw-Hill.
- Reason, James, and Alan Hobbs. 2003. *Managing Maintenance Error: A Practical Guide*. Burlington, VT: Ashgate.
- Rodríguez-Pérez, José. 2014. *The FDA and Worldwide Current Good Manufacturing Practices and Quality System Requirements Guidebook for Finished Pharmaceuticals*, Milwaukee, WI: ASQ Quality Press.
- Rodríguez-Pérez, José. 2021. *Quality Culture in the Pharmaceutical Industry*, Bayamón: Business Excellence Consulting.
- Rodríguez-Pérez, José, and Manuel Peña-Rodríguez. 2012. "Fail-Safe FMEA." *Quality Progress*, January 2012, 31–36.
- Wilson, Paul, Larry Dell, and Gaylord Anderson. 1993. *Root Cause Analysis: A Tool for Total Quality Management*. Milwaukee, WI: ASQ Quality Press.

USEFUL WEBSITES

https://ec.europa.eu/health/documents/eudralex_en

The body of European Union legislation in the pharmaceutical sector is compiled here.

<http://www.asq.org>

The American Society for Quality (ASQ) is the world's leading membership organization devoted to quality. This site provides useful information, resources, and links for quality topics.

<http://www.fda.gov>

This is the entry page to the US Food and Drug Administration.

<http://www.fda.gov/ora>

This page contains significant ORA documents (consent decrees, 483 forms, establishment inspection reports, and many more regulatory documents) under its ORA FOIA Electronic Reading Room.

<http://www.fda.gov/iceci/enforcementActions/Warningletters/default.htm>

This is the place to see FDA-published warning letters sent to regulated firms.

<http://www.fda.gov/safety/Recalls/default.htm>

This section includes the most significant product actions over the last five years based on the extent of distribution and the degree of health risk. Here, you will find a listing of FDA and industry press releases regarding product recalls. It includes a link to weekly FDA enforcement reports.

<http://www.bec-global.com>

Author's website.

<http://www.calidadpr.com>

Author's page devoted to general quality topics (in Spanish).

<http://www.ich.org>

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 registration.

<http://www.imdrf.org>

The International Medical Device Regulators Forum (IMDRF) was conceived in February 2011 as a forum to discuss future directions in medical device regulatory harmonization. It is a voluntary group of medical device regulators from around the world who have come together to build on the strong foundational work of the Global Harmonization Task Force on Medical Devices (GHTF) and to accelerate international medical device regulatory harmonization and convergence.

Acronyms

CAPA	Corrective and preventive action
CDER	FDA's Center for Drug Evaluation and Research
CDRH	FDA's Center for Devices and Radiological Health
CFR	US Code of Federal Regulations
CGMP	Current good manufacturing practice
EU	European Union
FAR	Field alert report
FDA	Food and Drug Administration
FMEA	Failure modes and effects analysis
FTA	Fault tree analysis
GHTF	Global Harmonization Task Force
HACCP	Hazard analysis and critical control point
ICH	International Conference on Harmonization
IMDRF	International Medical Device Regulators Forum
ISO	International Standardization Organization
MDR	Medical device reporting
NCR	Nonconformance report
OOC	Out of control
OOS	Out of specification
OOT	Out of trend
ORA	FDA's Office of Regulatory Affairs
QC	Quality control
QCU	Quality control unit
QMS	Quality management system

QSIT	FDA's quality system inspection technique
QSR	FDA's quality system regulations
RCA	Root cause analysis
SPC	Statistical process control

Glossary

action threshold: A statistical limit based on historical data used to indicate an adverse trend, requiring an action. See OOC.

adverse trend: A general drift or tendency in a set of data to exceed established limits over an established period.

annual product review: An evaluation, conducted at least annually, that assesses the quality standards of each drug product to determine the need for changes in the drug product specifications or manufacturing or control procedures.

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 products and other quality problems (preventive action).

CAPA plan: Encompasses the identification of corrective and/or preventive actions, their verification and/or validation (prior to implementation), their implementation, and finally the evaluation of the plan's effectiveness.

causal factor: Any failure (human, equipment, or material/component) that directly caused the incident, allowed it to occur, or allowed the consequence to be worse.

concession: A special approval granted to release a nonconforming product for use or delivery. Concessions are usually limited by time and quantity and tend to specify that nonconforming characteristics may not violate specified limits.

continuous improvement: Ongoing activities to evaluate and positively change products, processes, and the quality system to increase effectiveness.

control limit (CL): A horizontal line on a control chart that represents a boundary for a process. If the process strays beyond a control limit, it may be out of control.

correction: Action to eliminate a detected nonconformity. Corrections typically are one-time fixes. A correction is an immediate solution such as repair or rework. 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 cause.

current good manufacturing practices (CGMP): A set of current regulations for the control and management of manufacturing and quality control of foods, pharmaceutical products, and medical devices. GMPs are guidelines that outline the aspects of production that would affect the quality of a product. Many countries have created their own GMP guidelines that correspond with their legislation.

customer: A person or organization (internal or external) that receives a product or service anywhere along the product's life cycle.

discrepancy: Datum or result outside of the expected range; an unfulfilled requirement. May be called nonconformity, defect, deviation, out of specification, out of limit, out of trend.

effectiveness: The degree to which a planned effect is achieved. Planned activities are effective if these activities are realized. Similarly, planned results are effective if these results are achieved. For example, an effective process is one that realizes planned activities and achieves planned results. Similarly, an effective set of characteristics or specifications is one that has the potential to realize planned activities and achieve planned results.

effectiveness evaluation: Documented process to establish that an action was effective and accomplished the objective that was intended.

efficiency: A relationship between results achieved (outputs) and resources used (inputs). Efficiency can be enhanced by achieving more with the same or fewer resources. The efficiency of a process or system can be enhanced by achieving more or getting better results (outputs) with the same or fewer resources (inputs).

harm: Damage to health, including damage that can occur from the loss of product quality or availability (ICH Q9).

investigation: Thorough, timely, unbiased, well-documented, and scientifically sound process used to discover the root causes of the problem.

metric: A quantitative measurement that is collected, recorded, and analyzed to determine whether quality system goals and objectives have been met or exceeded or failed to meet the requirements.

monitor: To observe and check over a period; to maintain regular close observation over a process.

nonconformance: Nonfulfillment of specified requirements.

nonconformity: A deficiency in a characteristic, product specification, process parameter, record, or procedure that renders the quality of a product unacceptable, indeterminate, or not according to specified requirements.

objective evidence: Data that show or prove that something exists or is true. Objective evidence can be collected by means of observations, measurements, tests, or any other suitable method.

out of control (OOC): Any data points outside of control chart limits that represent the natural boundaries of the process.

out of specification (OOS): Test results (in process and final) that fall outside the established specifications or acceptance criteria.

preventive action: Action to eliminate the cause of a potential nonconformity or other undesirable potential situation. The preventive action should prevent the occurrence of the potential cause.

product/service: The intended results of activities or processes; products/ services can be tangible or intangible.

quality: The degree to which a set of inherent characteristics fulfills requirements. A measure of a product's or service's ability to satisfy the customer's stated or implied needs.

quality assurance: Proactive and retrospective activities that provide confidence that requirements are fulfilled.

quality control: The steps taken during the generation of a product or service to ensure that it meets requirements and that the product or service is reproducible.

quality management: Coordinated activities to direct and control an organization with regard to quality.

quality management system (QMS): Management system to direct and control an organization with regard to quality.

quality objectives: Specific measurable activities or processes to meet the intentions and directions as defined in the quality policy.

quality plan: The documented result of quality planning that is disseminated to all relevant levels of the organization.

quality planning: A management activity that sets quality objectives and defines the operational and/or quality system processes and the resources needed to fulfill the objectives.

quality policy: A statement of intentions and direction issued by the highest level of the organization related to satisfying customer needs. It is similar to a strategic direction that communicates quality expectations that the organization is striving to achieve.

quality system: Formalized business practices that define management responsibilities for organizational structure, processes, procedures, and resources needed to fulfill product/service requirements, customer satisfaction, and continuous improvement.

quality system regulations (QSR): US medical devices regulations (Title 21 CFR §820).

requirement: Need or expectation that is stated, generally implied, or obligatory.

rework: Action taken on a nonconforming product so that it will fulfill the specified requirements before it is released for distribution.

risk: The combination of the probability of occurrence of harm and the severity of that harm.

risk assessment: A systematic process for organizing information to support a risk decision that is made within a risk management process. The process consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards.

risk management: The systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating, and reviewing risk.

root cause: A gap in a process input or supporting business system that is, at least partly, responsible for the incident. It is the basic reason causal factors occur and/or persist.

root cause analysis (RCA): Analysis necessary to determine the original or true cause of a system, product, or process nonconformity. This effort extends beyond the effects of a problem to discover its most fundamental cause.

specification: Any requirement with which a product, process, service, or other activity must conform.

stakeholder: An individual or organization with ownership or interest in the delivery, results, and metrics of the quality system framework or business process improvements.

trend: A sequence or pattern of data. Analysis of a trend is performed to detect a special cause amidst the random variation of data.

timeliness: A time frame commensurate with the risk and magnitude of the issue; considered reasonable by a company that is concerned with protecting the public health.

validation: Confirmation, through the provision of objective evidence, that the requirements for a specific intended use or application can be consistently fulfilled.

verification: Confirmation, through the provision of objective evidence, that specified requirements have been fulfilled.

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About the Author

Dr. José (Pepe) Rodríguez-Pérez is the president of Business Excellence Consulting Inc. (BEC), a Puerto Rico-based global consultant, training, and remediation firm in the areas of regulatory compliance, risk management, and regulatory training in the FDA-regulated sector. He's also president of BEC Spain. Dr. Rodríguez-Pérez is a biologist and earned his doctoral degree in biology from the University of Granada (Spain). He served as professor and director of the Microbiology Department at one of the Puerto Rico schools of medicine, and he also served as Technical Services manager at a manufacturing plant of *Abbott Laboratories* in Puerto Rico. From 2003 to 2012, he was professor for graduate studies of the Polytechnic University of Puerto Rico, and he served as a Science Advisor for the FDA from 2009 to 2011.

Dr. Rodríguez-Pérez is a senior member of ASQ, as well as a member of AAMI, ISPE, PDA, and RAPS. He is an ASQ-certified Six Sigma Black Belt, Quality Manager, Quality Engineer, Quality Auditor, Quality HACCP Auditor, Biomedical Auditor, and Pharmaceutical GMP Professional. He is also the author of the best-selling books *CAPA for the FDA-Regulated Industry*, *Quality Risk Management in the FDA-Regulated Industry*, *The FDA and Worldwide Current Good Manufacturing Practices and Quality System Requirements Guidebook for Finished Pharmaceuticals*, *Human Error Reduction in Manufacturing*, and *Data Integrity and Compliance*, all available from ASQ Quality Press. Contact Dr. Rodríguez-Pérez at pepe.rodriguez@bec-global.com.



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