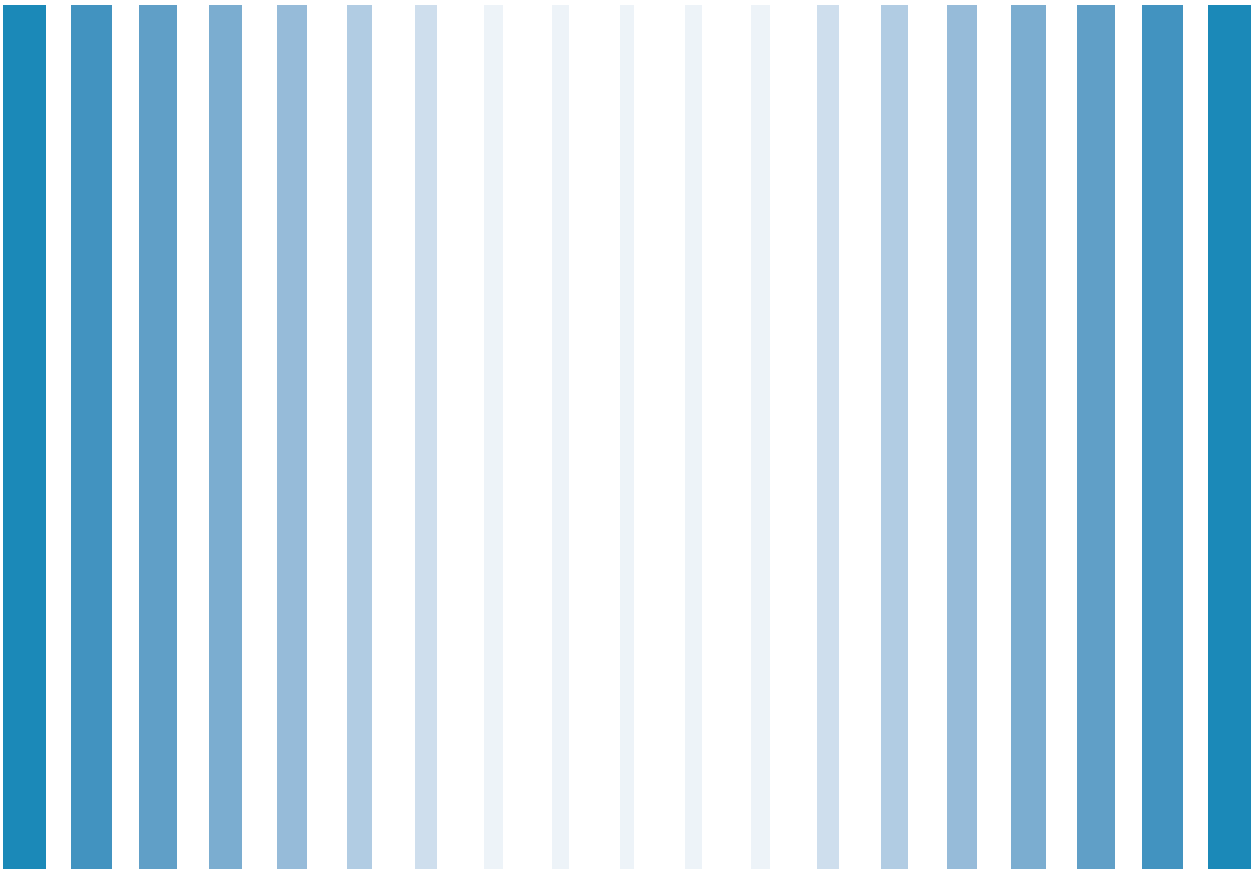
ISPE – PDA Guide to Improving Quality Culture in Pharmaceutical Manufacturing Facilities



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Background

Quality Culture has always been important within pharmaceutical manufacturing operations. Strong companies know this and have invested resources in systems and personnel to support and promote a focus on quality processes, product quality, and meeting patient needs. More recently, health authorities have placed additional emphasis on quality culture by including it in guidance documents and inspection protocols like the PIC/S Data Integrity Guidance, ***(1)*** FDA New Inspection Protocol Project (NIPP), ***(2)*** and the MHRA Data Integrity Guideline. ***(3)***

Both ISPE and PDA have developed information and resources to help pharmaceutical companies better understand why quality culture is important and how to assess the current situation within a site or organization. *The ISPE Cultural Excellence Report* ***(4)*** shares the vision of quality culture improvements across six dimensions, utilizes a 19-behavior cultural maturity assessment, outlines a series of practices and tools to support implementation, and provides a practical frame of reference for companies that want to build healthy quality cultures within their organizations. The PDA Quality Culture Assessment Program ***(5)*** is based on a Maturity Model containing 21 quality culture metrics and offers training for assessors, a PDA-administered all employee survey, and access to composite benchmarking results for comparison with peer sites. By using either approach, a company can identify and prioritize areas within their own culture that need improvement. Many companies have specific cultural and quality system assessment processes which they have developed internally and would benefit from the use of a reference guide to advance the maturity of a specific framework element.

Members of the ISPE and PDA culture task forces have come together to develop this reference guide that identifies specific aspects of quality systems and culture and recommendations for tools, techniques, and processes. The purpose of this guide is not to provide complete training or implementation of any tools or to be an all-inclusive list; instead, the guide is intended to serve as a resource with links to additional information for the most commonly used tools. The tools included in this reference guide are accessible without fee. Different approaches or tools may be better suited for some problems or situations, and it is up to each user of this guide to determine what works best in each circumstance.

The guidance is divided into two sections: "Root Cause Analysis Tools and Approaches" and "Human Error Analysis Tools and Approaches."

Anyone who wishes to contribute to future editions of this guide or suggest additional topics should contact member services at ISPE at ask@ispe.org or PDA at info@pda.org.

In closing, while the focus of many CAPA systems in practice today is on major compliance breaches, consideration should also be given to applying these techniques proactively to smaller non-conformance or out-of-trend events that often present risks to product quality, waste time and money, or more importantly, a missed opportunity for learning. Moreover, nothing guarantees that some of these more minor events will not recur with more severe consequences under unfavourable circumstances at some time in the future. We hope that you find this practical guide not only user-friendly, but useful in delivering lasting solutions to the challenges involved in managing the many sources of variations encountered.

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Root Cause Analysis Guide Introductory Remarks

The Benjamin Franklin axiom, "An ounce of prevention is worth a pound of cure," points to a way for the pharmaceutical industry to strengthen the cultural foundations that underpinning the values and behaviors that deliver high-quality products to patients every day. The mark of a mature culture within an organization is how it deals with ever-increasing complexity as failures and deviations arise. Also important is whether it proactively evaluates potential risks to prevent failures or recurring deviations or reactively detects and corrects failures after they have occurred. Twenty-first century Pharmaceutical Quality Systems (PQS) require a more balanced approach to prevent and cure. Corrective and Preventive Action (CAPA) systems are designed to implement and record both corrective and preventative actions. ICH Q10 goes further about effective CAPA processes by recommending:

> *A structured approach to the investigation process should be used with the objective of determining the root cause. The level of effort, formality, and documentation of the investigation should be commensurate with the level of risk, in line with ICH Q9. CAPA methodology should result in product and process improvements and enhanced product and process understanding.* ***(6)***

This practical reference guide aims to support organizations in implementing a more structured approach to their investigation processes, which can enhance patient safety and deliver value to the business. RCA is the process of determining the underlying causes of a problem to identify appropriate corrective or preventive actions and forms a significant part of any organization's continuous improvement program. A common problem encountered within CAPA systems is the lack of rigor applied to identifying the true root cause of failure events. This leads to situations where "effects" of a given failure or "causal factors" (those factors that could potentially have prevented the incident or mitigated its consequences) are identified and corrected, rather than the underlying cause. These symptoms of failure are often more visible and easily reported, while the actual root causes of the problem may be submerged, unknown, and therefore not addressed. Not surprisingly, this often leads to recurrence of the failure at another time or in another context in the organization.

RCA is a systematic problem-solving process of unearthing these root causes to apply lasting solutions. Effective RCA requires the application of critical thinking, a multi-disciplinary knowledge seeking approach applied across the organization, site, and even shift rotation. To assist pharmaceutical firms to improve their current problem-solving approaches, ISPE and PDA have collaborated to collect a range of RCA tools which can be applied in the search for "true root cause." Not all tools are equal, and familiarization will build skills in their use.

Different approaches or tools may be better suited for some problems or situations. It is up to each user of this guide, therefore, to determine what works best in each circumstance. In many situations, a combination of RCA tools will provide the most comprehensive results. Another best practice is for a firm to select a set of tools, not more than six, that are used repeatedly to build expertise and consistency of results.

This is not intended to be an all-inclusive list but to highlight many of the commonly used approaches and provide guidance on how and when to use each. The tools within this guide are arranged according to difficulty rating for each tool included. They are accessible without fee. Introducing the experiences of people provides a valuable link to the "know-how" of those involved in experiencing the problem. For this purpose, accompanying each RCA tool or technique described in the guide are recommendations for best applications "✓" and cautions or special considerations for use "⚠." Also included are links to further discussion and resources.

Root Cause Analysis Tools and Approaches

"If you are unable to understand the cause of a problem, it is impossible to solve it." — Naoto Kan

Low Complexity				
Tool/Description	**Useful For**	**✓**	**⚠**	**For Further Reading**
Silent Brainstorming of Undesirable Effects; Affinity Diagrams A list of problems that may be gathered into like categories through affinity and mapped in a cause-and-effect diagram/tree or a causal circle. An Affinity Diagram is used to generate and organize information into categories. It allows you to represent the structure of big and complex factors which impact a problem into smaller groups.	Lower complexity events, simple solutions, problem identification, and affinization.	Use as a lead into other more complex tools	Participants knowledge and background are important	https://asq.org/quality-resources/affinity https://www.sixsigmadaily.com/the-affinity-diagram-tool/
Five (5) Whys An iterative interrogative technique used to explore cause-and-effect relationships for a proplem; it involves asking "Why?" at least five successive times to drill down through multiple causal effects to underlying root causes.	Lower complexity events, simple solutions.	Focus on the questions Do immediately after the event at the place of occurrence Use simple and complete sentences to ensure accurate "Whys"	Tool is not as structured as others Ensure purpose is to uncover why events occurred vs. who is to blame Need additional tools for complex events	http://asq.org/healthcare-use/why-quality/five-whys.html https://www.mindtools.com/pages/article/newTMC_5W.htm
Barrier Analysis This method considers the pathways through which a hazard can affect a target and then characterizes the performance of actual or potential barriers or controls. A barrier is anything in place that prevents an error from occurring or assures it will be detected, e.g., physical separation, in-process controls, administrative or procedural controls, or automation. Potential hazards are identified at each point in a process map, then current barriers are identified and effectiveness evaluated. Also captures ways to strengthen existing or add new barriers. ***(7)***	Low complexity events; activities that include multiple departments, handoffs, or rework cycles; white space.	Easy to use and apply, requires minimal resources Works well in combination with other methods Results translate naturally into corrective action recommendations	Must have a process map to begin Sometimes subjective in results Cross check with other RCA methods to ensure less obvious causes are not missed.	http://www.bill-wilson.net/root-cause-analysis/rca-tools/barrier-analysis

Medium Complexity				
Tool/Description	**Useful For**	**✓**	**⚠**	**For Further Reading**
Process Mapping According to ASQ, "A picture of the separate steps of a process in sequential order… Elements that may be included are a sequence of actions, materials or series entering or leaving the process (inputs and outputs), decisions that must be made, people who may become involved, time involved at each step, re-work loops, and/ or process measurements." ***(8)***	Events likely related to activities that include multiple departments, handoffs, or re-work cycles; white space; data [integrity] life cycle mapping/ review; can be a starting point for further analyses.	Use additional mapping types, such as process test bed or swim lanes Valuable for investigation reports and training purposes Use cross-functional group	Be mindful of differences between shifts/ teams Often requires use of additional tools/analysis to determine root cause **Beware:** process maps created in a meeting room are rarely accurate	https://asq.org/quality-resources/flowchart
Cause and Effect Matrix (C&E Matrix) Relates the process inputs to process outputs or causes to effects. Inputs and outputs are rated by their interaction impact. This determines what key process input variables should be given the most attention or may aid in the focus on root cause.	Simple events with discrete causes.	Great for use with technical teams	Use consistency in numerical values	https://sixsigmadsi.com/how-to-complete-the-ce-matrix/# https://blog.gembaacademy.com/2007/06/11/need-help-making-decisions/
Causal Circle Also known as Causal Loop, Causal Circle is a visual diagram that depicts how different system variables are interrelated using directional arrows to connect identified causes or Undesirable Effects (UDEs); helps distinguish causes from effects. Visually based results.	Simple events with discrete causes.	Great for use with creative teams Excellent tool for separating causes from effects May need to drill causes down further to RCA	Consistently ask "Does factor X cause factor Y to occur?" around the complete circle	https://thesystemsthinker.com/causal-loop-construction-the-basics/ https://www.isixsigma.com/tools-templates/cause-effect/causal-loop-diagrams-little-known-analytical-tool/
Causal Factors Tree Analysis Causal Factor Tree Analysis is a Root Cause Analysis technique used to record and display, in a logical, tree-structured hierarchy, all the actions and conditions (or Causal Factors) that were necessary and sufficient for a given consequence to have occurred. ***(9)***	Simple events with discrete causes.	Great for use with logical or visual learners May need to drill causes down further to RCA	Use consistency of causal factor hierarchy	https://www.bill-wilson.net/root-cause-analysis/rca-tools/causal-factor-tree-analysis

High Complexity				
Tool/Description	**Useful For**	**✓**	**⚠**	**For Further Reading**
Fishbone (Ishikawa) Diagram Tool Also called an Ishikawa Diagram or 6M Analysis, this tool separates all the potential causes of a specific event or problem into major categories; categories are often assigned as the 6Ms: manpower, machine, method, material, measurement, and milieu (often called environment or Mother Nature).	Moderate to high complexity events, equipment and microbiology related events.	Brainstorm to generate ideas Use affinity diagram to create a group-specific fishbone Look for "How did problem occur?", "How did the problem escape detection?", and "What occurred in the system that enabled the specific process break?"	**Must** use cross-functional team and culture of inclusion Manage interpersonal dynamics during creation Start with a clear and agreed upon problem statement Don't forget causal factors related to team or workplace environment/culture	http://asq.org/learn-about-quality/cause-analysis-tools/overview/fishbone.html https://www.mindtools.com/pages/article/newTMC_03.htm
Failure Mode Effects Analysis (FMEA) Failure Mode and Effects Analysis (FMEA) is a team-based proactive step-by-step approach for identifying all possible failures in a design, manufacturing, or assembly process or a product or service. According to the American Society for Quality (ASQ), " 'Failure modes' means the ways, or modes, in which something might fail. Failures are any errors or defects, especially ones that affect the customer, and can be potential or actual. 'Effects analysis' refers to studying the consequences of those failures." ***(10)***	Preventive tool for implementation of equipment/process/ product design, continuous improvement projects.	Complete the tool from left to right for each item Use after implementation to develop the control plan Also useful for CAPA effectiveness	**Must** use knowledgeable SMEs Requires high process/ product/ system knowledge	https://asq.org/quality-resources/fmea https://www.isixsigma.com/tools-templates/fmea/quick-guide-failure-mode-and-effects-analysis/
Fault Tree Analysis A model to visualize all potential technical faults that may occur for a piece of equipment, sorted by major categories. This analysis typically supports the creation of a control plan for the equipment. It is often performed prior to implementation of equipment/process.	Developing control plans for technical measures; identifying all potential events/faults for a standard process (e.g., packaging lines).	Use as a preventive tool Use for risk assessments for equipment or safety measures	SMEs for various aspects of process must be involved **Beware:** Simple fault trees are not likely complete or accurate	http://asq.org/quality-progress/2016/01/best-of-back-to-basics/what-is-a-fault-tree-analysis.pdf

Human Error Analysis Tools and Approaches

When investigating root causes of a problem or deviation, the analysis will frequently point to human error. While it is tempting to stop there and insert countermeasures such as "retrain the operator" or "update the SOP," human performance is inherently variable and dependent on the conditions of the environment, which means these tools and approaches alone are unlikely to lead to long-term, stable solutions.

A more in-depth analysis of the human factors behind the errors in any given process or problem should be conducted. Human error should not be the conclusion of a root cause investigation but the starting point. This analysis should also include a thorough understanding or assessment of the culture of a sub-team, working group, or organization. Research has shown the frequency of mistakes is increased by the stress or complexity of the environment. Once the human factors are well understood, actions such as error proofing, poka-yoke, or related engineering solutions can be put in place to reduce the potential for human error. Some resources and tools that can help with this analysis and improvement are listed below.

Low Complexity	
Poka-Yoke PokaYoke is a Japanese phrase that means error prevention; A "poka" is an inadvertent error and "yokeru" is Japanese for preventing. This system implements countermeasures that force actions to be carried out correctly, leaving no room for misunderstandings. Many solutions in Poka-Yoke tend to be simple, cheap, and effective and can be integrated into the product design or one of the process steps. ***(11)***	https://www.toolshero.com/quality-management/poka-yoke/
Medium Complexity	
Human Factors and their Optimization – Process Improvement Institute From the abstract, "This paper lists where focus should be placed (i.e., which human factors tend to be key) and provides proven ways to optimize these human factors so that the base human error rate at a site is as low as possible." ***(12)***	http://www.process-improvement-institute.com/_downloads/Human_Factors_and_their_Optimization_website.pdf
ABC Model "The Antecedent-Behavior-Consequence (ABC) Model is an approach that can be used to help people examine behaviors (they) want to change, the triggers of those behaviors, and the impact of those behaviors on negative or maladaptive patterns. In ABC Analysis, the antecedent, behavior, and consequence provide considered 'building blocks' in understanding, analyzing, and potentially changing how one acts. ABC charts can be used to provide 'snapshots' into the situation, potentially enabling further comprehension of the behavior." ***(13)***	https://www.betterhelp.com/advice/behavior/understanding-the-antecedent-behavior-consequence-model/

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