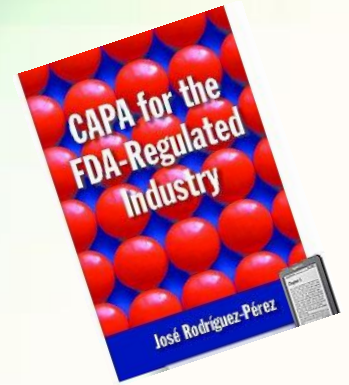


Passion for Quality



Importance of the CAPA System



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Purpose and Importance of the CAPA System

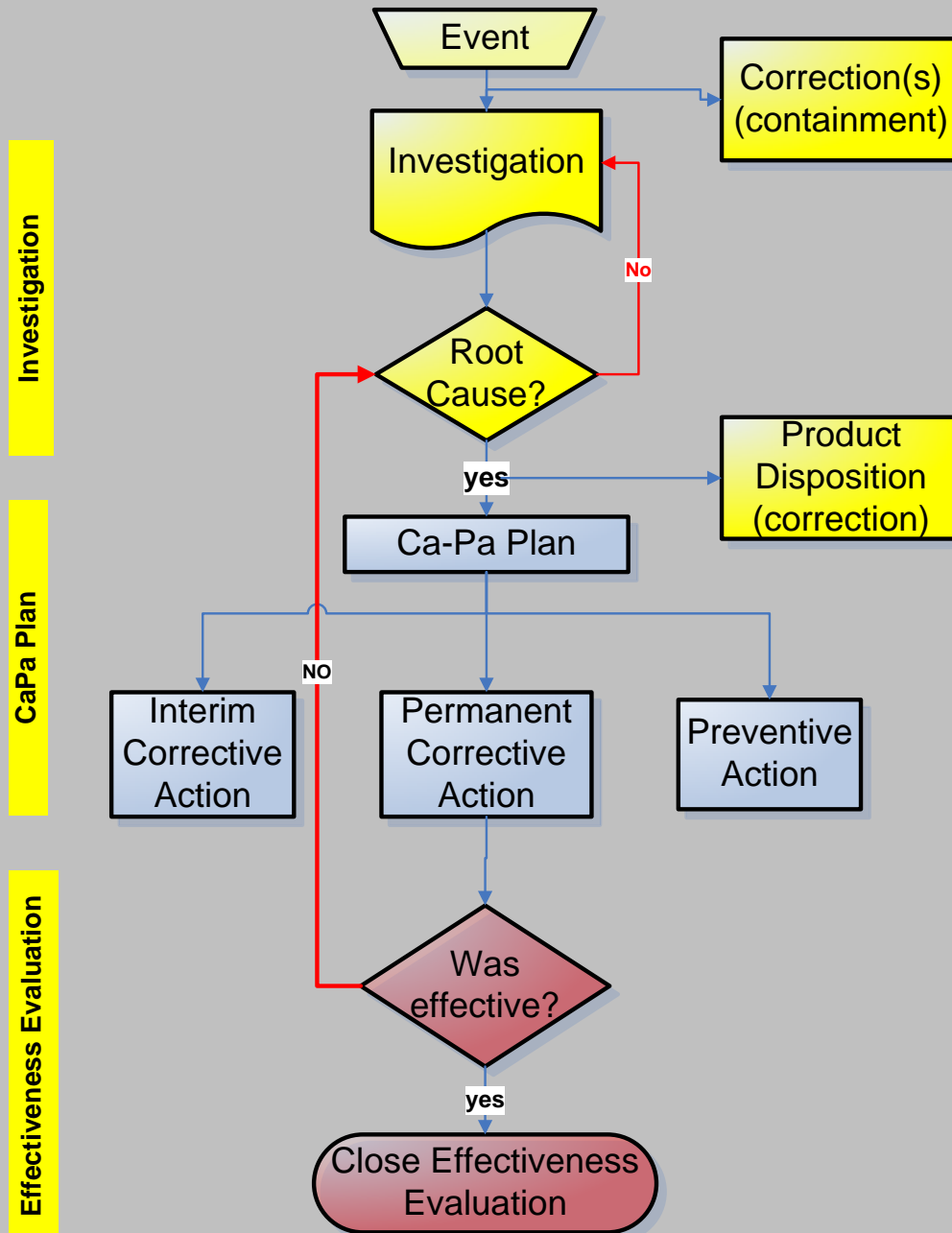
The purpose of the corrective and preventive action system is to collect and analyze information, identify and investigate product and quality problems, and take appropriate and effective corrective and/or preventive actions to prevent the recurrence of their causes.

Verifying or validating corrective and preventive actions, communicating these 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/minimizing product failures.

Definitions

- ★ **Correction / Remedial Action (containment)**– action to eliminate a detected nonconformity. Corrections typically are one-time fixes. A correction is an immediate solution.
- ★ **Corrective action** – action to eliminate the **cause(s)** of a detected nonconformity or other undesirable situation. The corrective action should eliminate (prevent) the **recurrence** of the issue.
- ★ **Preventive action** – action to eliminate the **cause(s)** of a potential nonconformity or other undesirable potential situations. The preventive action should eliminate or prevent the **occurrence** of the potential issue.

The CAPA System



Requirements (21 CFR 211.192)

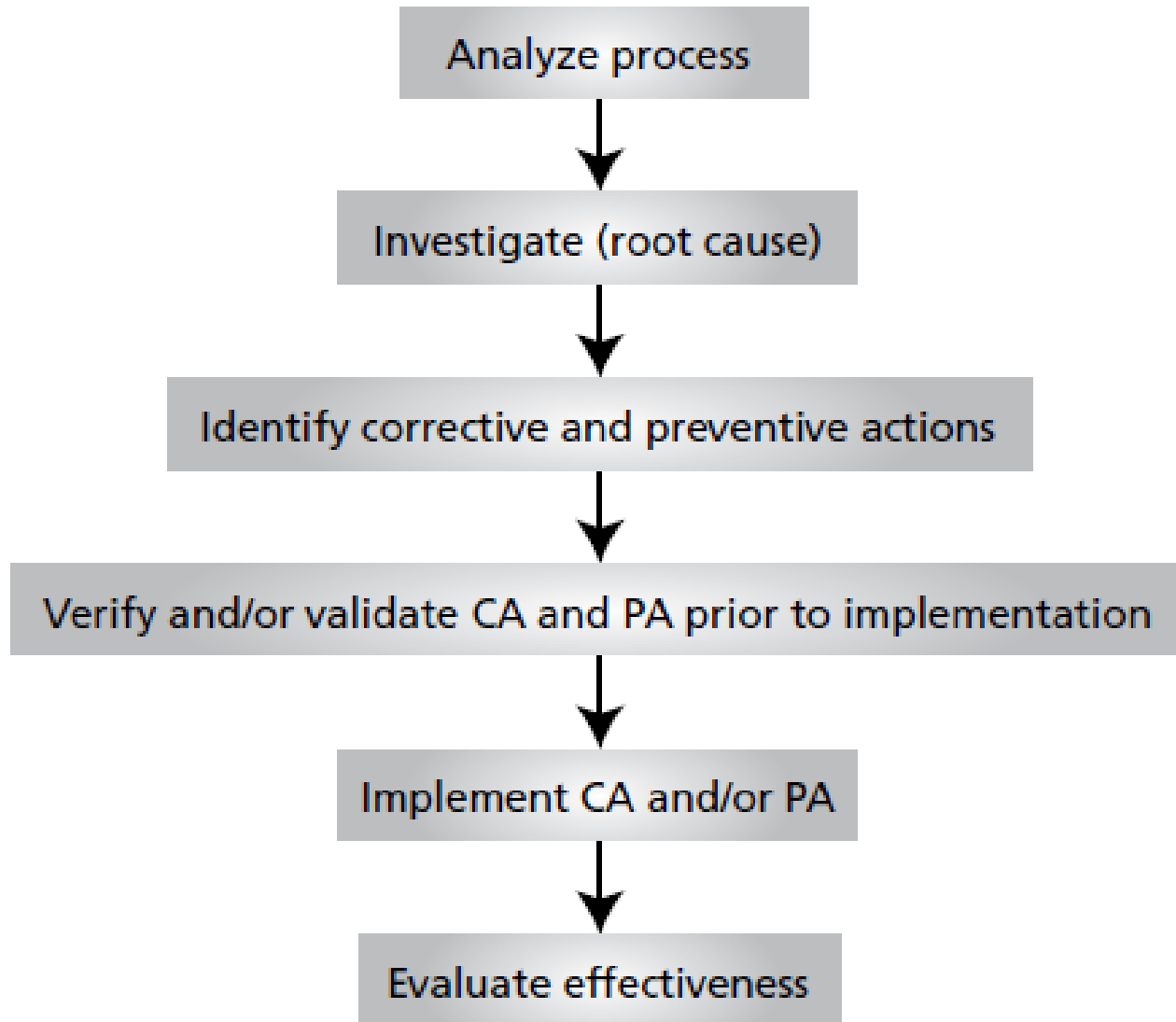
- Production record review

Any **unexplained discrepancy** 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 followup.**

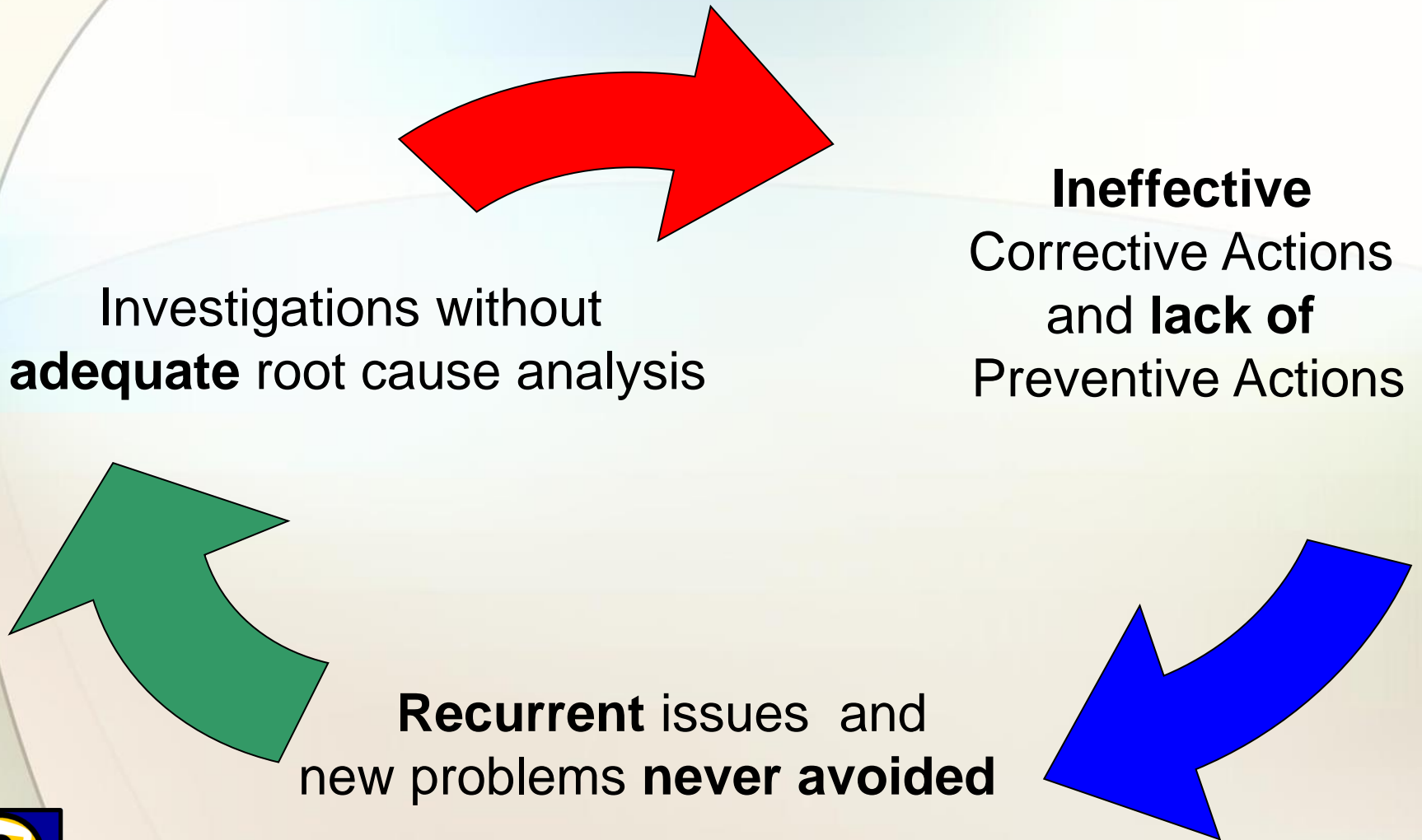
Requirements (21 CFR 820.100)

- (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...
 - (2) Investigating the cause of nonconformities ...
 - (3) Identifying the action(s) needed to correct and prevent recurrence ...
 - (4) Verifying or validating the corrective and preventive action to ensure that such action is effective ...
 - (5) Implementing ...
 - (6) Ensuring that information related to quality problems or nonconforming product is disseminated...
 - (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.**

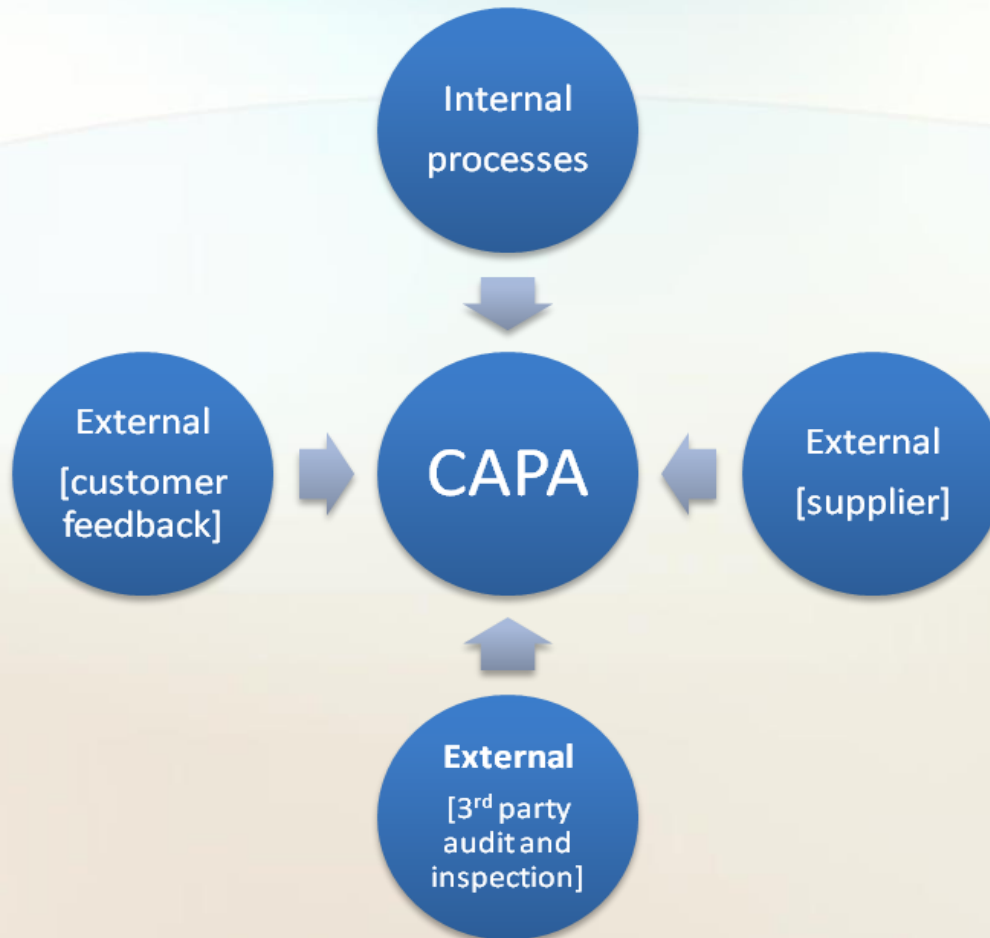
The CAPA Process Flow



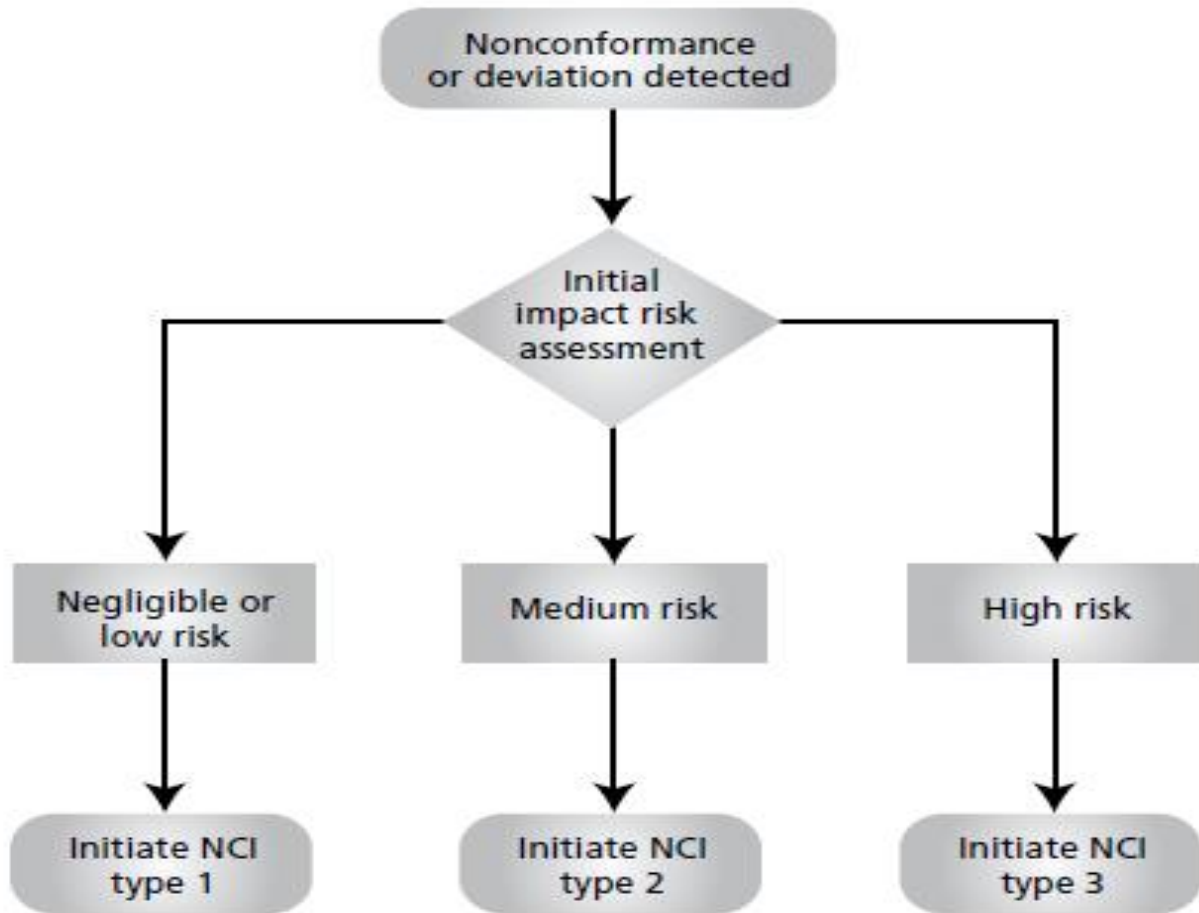
The Vicious Circle



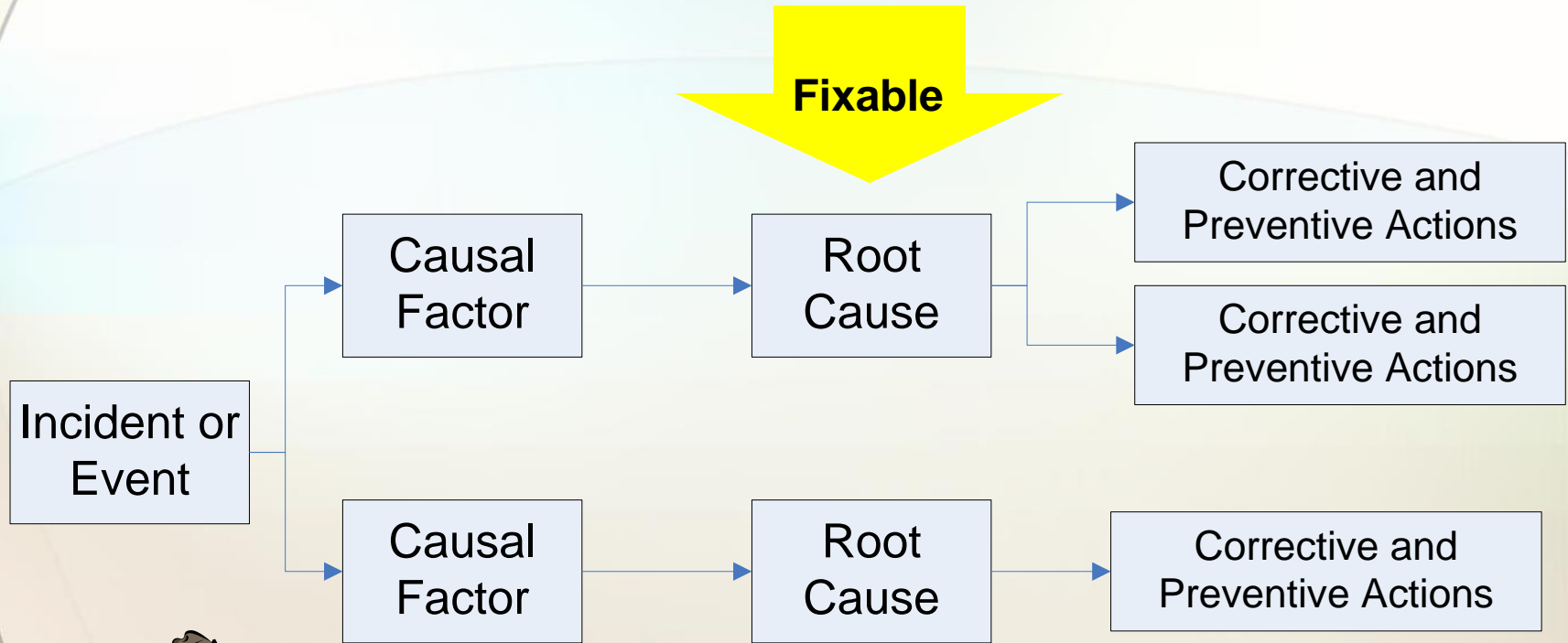
Feeders of the CAPA System



Risk Prioritization of Investigations



Root Cause Identification



A Healthy CAPA System Requires Resources and Time

**Team
Work**



Control Barrier Analysis

- ★ Barrier or control barrier analysis is the evaluation of current process control(s) to determine if those barriers pertaining to the problem you are investigating were present and effective.
- ★ Does the process have barriers (controls) to avoid this defect/problem?
 1. **Physical control barriers** (for example, dedicated equipment, etc.)
 2. **Administrative/management control barriers** (training, supervision, etc.)

If the answer is **yes**... Why did they fail?

If the answer is **no**... probable corrective action(s)

Elements of a CAPA Plan

Corrective Action(s). Must have at least one identified CA for each root cause already identified. Each Corrective Action must include the following information:

- ★ How this action will avoid the **recurrence** of the identified root cause?
- ★ If the proposed CA is not immediate, provide interim action(s)
- ★ **Implementation Verification:** how, when and by whom
- ★ **Effectiveness Check:** how, when and by whom
- ★ Can this action be extended to other product/process/system not yet affected by this root cause? If yes, open a Preventive Action.

Elements of a CAPA Plan cont.

Preventive Action(s). Should have at least one identified PA for each root cause already identified. Each Preventive Action must include the following information:

- ★ How this action will avoid the **occurrence** of the identified root cause?
- ★ If the proposed PA is not immediate, provide interim action(s)
- ★ **Implementation Verification:** how, when and by whom
- ★ **Effectiveness Check:** how, when and by whom

CaPa Plan Phase

CAPA Plan Best Practices

- Time is needed to analyze and develop effective actions.
 - Between two and four weeks is a reasonable timeframe to develop a CAPA plan.
- Avoid the use of “Analyze”, “Evaluate”, “Assess” or any synonymous as preventive actions. Most of the time, such analysis and evaluations do not reach any further. It is one of the main reasons for the lack of real preventive actions in our industry.
 - These assessments (i.e. “evaluate if any other document need to be changed”..) are performed during this CAPA plan timeframe and their results (i.e. “seven documents need to be changed”) is the true preventive actions to be implemented.

Corrective or Preventive?

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 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• Implement new (enhanced) processes

Effective Corrective and Preventive Actions?

- **CA:** to analyze the manufacturing instructions for all products .
- **PA:** Evaluate the possibility to identify any enhancement to the coating process for XXX product
- Reason for the ninth extension of a CA: more time is needed (same reason for the previous eight extensions)

Effectiveness Evaluation Phase: Timeliness

- The timeframe for this evaluation must be established case by case. Some firms established a fixed period of time (one month, three months, etc.) for all of their effectiveness evaluation, instead of correlating the period of time with the frequency of the process under evaluation.

Effectiveness Evaluation Best Practices:

- Use the “double-digits” rule of thumb: allow enough time to permit the evaluation of at least ten repetitions of the process under evaluation.
 - If the process runs every month, then one year could be a reasonable period of time to determine effectiveness
 - If the process is performed weekly, then three months should be enough
 - For daily process, one month is a good period of time to determine the effectiveness.

How to Measure the Effectiveness of Training Efforts

The four levels of evaluation (Kirkpatrick):

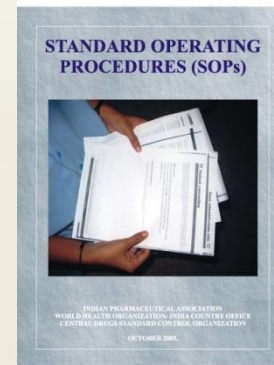
1. Evaluating reaction
2. Evaluating learning
3. Evaluating behavior
4. Evaluating results



Human Factors related to Training



- **Training evidence?**
 - *Trained in the current version of the procedure?*
- **Was effective?**
 - *Adequate content?*
 - *Adequate training delivery methodology?*
 - *Adequate training environment?*
 - *Adequate training instructor?*
 - *Adequate language?*
 - *Enough practice?*



Human Errors: Key Points to Consider

- ✓ Human errors are not root causes
- ✓ Human errors are symptoms or consequences of deeper causes
- ✓ Refrain from use **human error** (or procedure not followed or similar) as a **root cause** and **retraining** (refresher, awareness, counseling, orientation, etc.) as a **corrective action**

CAPA Effectiveness Examples

Root Cause	Corrective Action	Effectiveness Verification
Lack of robustness of test method X	Re-validate test method X Fixing similar test methods for other products will be an adequate preventive action Interim action:	a) Validation data b) Monitor next ten batches and use data to demonstrate that the testing results for X have lower variability; or they are closer to target, or....

Some Examples of Interim Actions

Corrective Action	Interim Action
<ul style="list-style-type: none">• Change a document• Validation or characterization (because the current process is not optimal)	<ul style="list-style-type: none">• Provide the same instructions using a “temporary” Planned Deviation until change control is implemented• Increase sampling quantities and frequency to provide additional confidence of the quality of the material manufactured using the current sub-optimal process



CAPA Effectiveness Examples

Root Cause	Corrective Action	Effectiveness Verification
Lack of instructions (no procedure) to perform CAPA Effectiveness evaluation	Create a procedure for CAPA Effectiveness Verification	Not necessary. It's impossible that the same root cause recurs What if the new procedure is incomplete?

CAPA Effectiveness Examples

Corrective Action	Effectiveness Verification
<p>Operators must be <u>retrained</u> in SOP-123 to clarify instructions for the capsule filling machine ABC</p>	<p>During the next month, a performance evaluation of 15 operators (five from each shift, randomly selected) will be performed to verify the correct use of SOP-123 instructions.</p> <p>This task will be completed using the attached check list which reproduces SOP sequence of instructions. CA will be considered effective if all evaluated operators were following the procedure.</p>



CAPA Effectiveness Examples

Root Cause	Corrective Action	Effectiveness Verification
Lack of adequate maintenance of the induction sealer created customer complaints (open seals)	Modify the PM of the equipment to include a daily verification of parameter X	a) Establish a sampling plan to monitor the next 20 lots sealed b) Monitor customer complaints during three months once the new PM is implemented

CAPA Effectiveness Examples

Corrective Action	Effectiveness Verification
<p>Revise SOP 333 to include the use of sterile gloves and surgical mask during sampling</p>	<p>During the next two months, a performance evaluation of 15 associates from each area performing this type of sampling (five from each shift, randomly selected) will be performed to verify the use of sterile gloves and surgical masks. CA will be considered effective if all evaluated operators were following the procedure.</p>

Eleven Biggest CAPA Opportunities

1. Timeliness
2. Everything is an Isolated Event
3. Root Cause not identified
4. Correcting the Symptoms Instead of the Cause
5. Lack of Interim Corrective Actions
6. Root Causes Identified but not Corrected
7. Lack of True Preventive Actions
8. Lack of Effectiveness Verification of the Action Taken
9. Multiple CAPA Systems without Correlation
10. Abuse of Human Error and Retraining
11. Over-customization of the CAPA System

Muchas Gracias

Presentation available at

<http://www.calidadpr.com/enlaces.html>