Conducting CAPA Investigations

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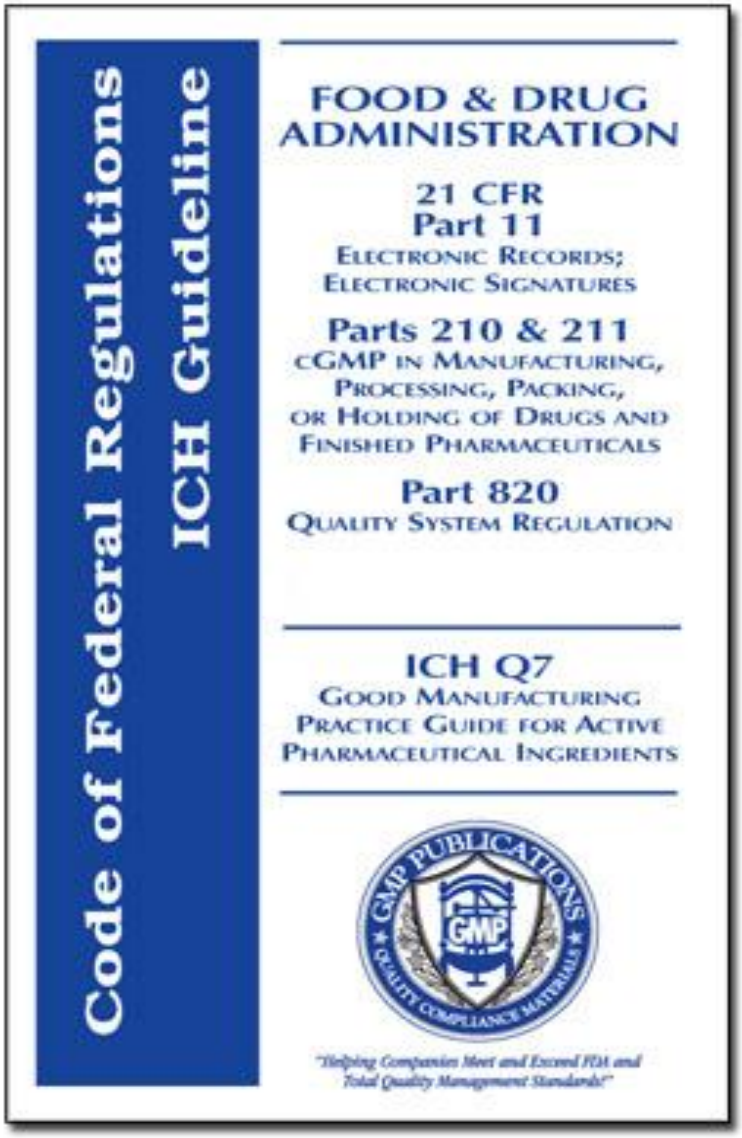
Webinar Overview

- Regulations
- Historical Problems
- CAPA Process Flow
- Investigation
- Correction, Corrective and Preventive Action
- Effectiveness
- CAPA Timeliness
- Tracking and Trending
- Management Review
- Lessons Learned

Regulations

Regulations

- Required by law
  - Food, Drug and Cosmetic Act
  - 21 CFR 211
  - 21 CFR 820
  - EudraLex
  - ISO
  - ICH
  - GHTF



Food, Drug and Cosmetic Act

- SEC. 501. [21 USC § 351] (a)(2)(B)
  - a drug shall be deemed to be adulterated if **the methods used in**, or the **facilities or controls used for**, its **manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice** to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.

21 CFR 211.22

(a) There shall be a quality control unit that shall have the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, and the authority to review production records to assure that no errors have occurred or, **if errors have occurred, that they have been fully investigated.** The quality control unit shall be responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company.

21 CFR 820

820.100: "Investigating the cause of nonconformities relating to product, processes, and the quality system"

820.198: "Any complaint involving the possible failure of a device, labeling, or packaging to meet any of its specifications shall be reviewed, evaluated, and investigated."

820.90: "The evaluation and any investigation shall be documented."

820.100: "**Corrective and preventive action**. (a)Each manufacturer shall establish and maintain procedures for implementing **corrective and preventive action**"

EudraLex Volume 4

- A Pharmaceutical Quality System appropriate for the manufacture of medicinal products should ensure that:
  - 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.
  - An appropriate level of root cause analysis should be applied during the investigation of deviations, suspected product defects and other problems.
  - Appropriate **corrective actions and/or preventative actions (CAPAs)** should be identified and taken in response to investigations.
  - A review of all batches that failed to meet established specification(s) and their investigation.
  - A review of all quality-related returns, complaints and recalls and the investigations performed at the time.

Other

- International Organization for Standardization (ISO)
  - ISO 13485: Quality Management for Medical Devices
- International Conference on Harmonization (ICH)
  - Q10: Pharmaceutical Quality System
- Global Harmonization Task Force* (GHTF)
  - Quality management system –Medical Devices – Guidance on corrective action and preventive action and related QMS processes

*The International Medical Device Regulators Forum (IMDRF) is continuing the work of the Global Harmonization Task Force (GHTF).

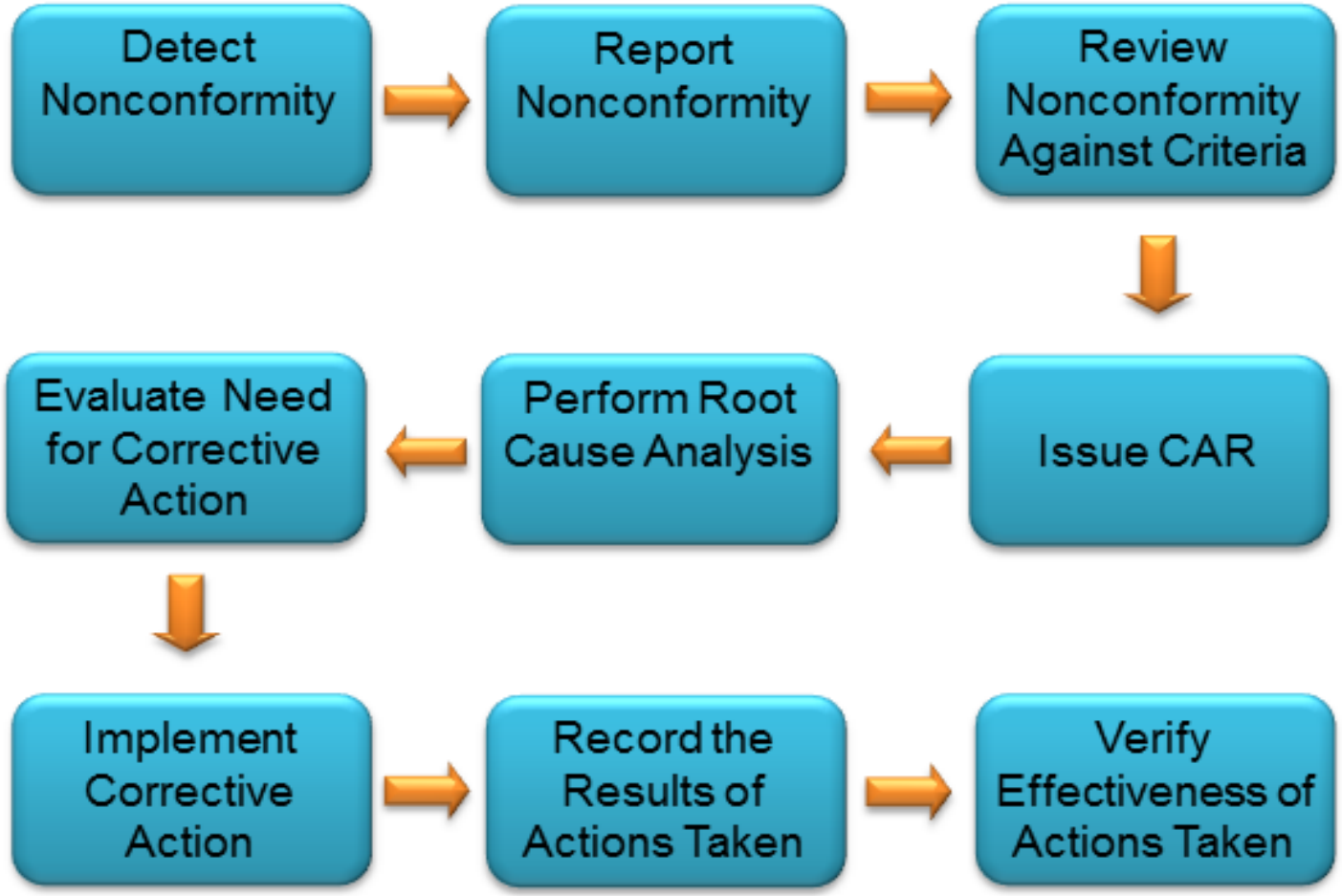
Historical Problems

Inspectional Observation Summary for CAPA

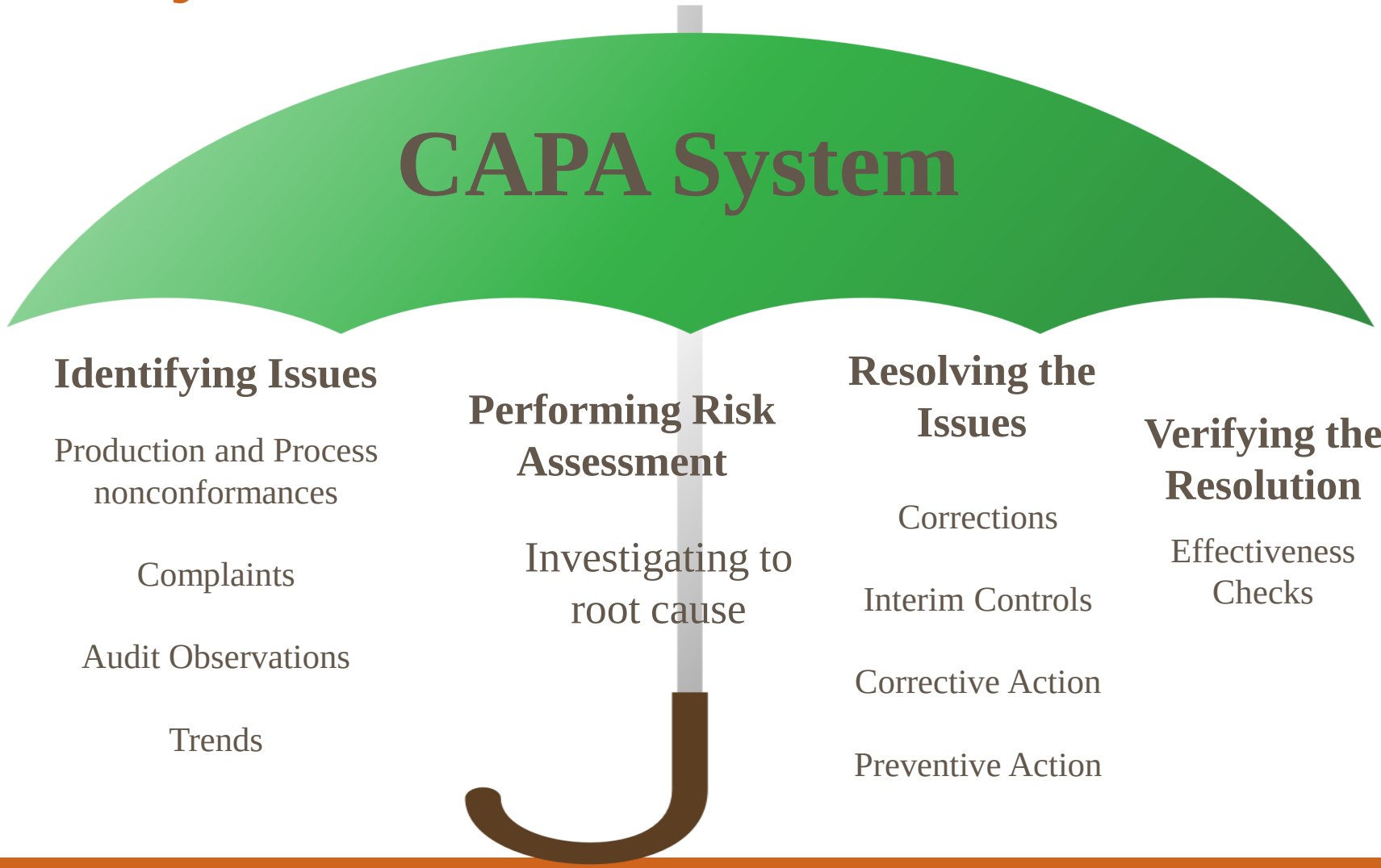
Year	Devices	Pharmaceuticals
2015	483's – 1008 #1 Citation – CAPA/Investigations	483's – 678 #3 Citation – CAPA/Investigations
2014	483's – 972 #1 Citation – CAPA/Investigations	483's – 645 #3 Citation – CAPA/Investigations
2013	483's – 1099 #1 Citation – CAPA/Investigations	483's – 690 #2 Citation – CAPA/Investigations
2012	483's – 1090 #1 Citation – CAPA/Investigations	483's – 787 #2 Citation – CAPA/Investigations
2011	483's – 1035 #1 Citation – CAPA/Investigations	483's – 758 #4 Citation – CAPA/Investigations

What is CAPA?

The CAPA Process



Key Point to Remember



Risk Assessment

- What is the impact of the issue to the health and safety of the patient and/or user.
- What is the scope of the issue:
  - Product in the field
  - Multiple lots
  - Multiple locations
  - Frequency of occurrence
  - Identified in Hazard Analysis
- Use your Risk Management Tools.

Investigations

If an initial evaluation and risk assessment indicates, a documented investigation consistent with the significance of the quality issue, is performed to determine Root or Probable Cause.

Investigations continued

- Initial Risk Assessment will determine the:
  - Depth of investigation:
    - Simple issues = simple investigations
    - Complex/safety critical issues = detailed investigations
  - Urgency of the investigation.

- Obtain Quality Management support

Investigations continued

- Write an Investigation Plan.
  - Identify an Owner (process or event).
  - Engage a team if applicable.
  - Determine tools to be used.
  - Determine areas to be investigated.
  - Determine how to investigate.
  - Establish a timeline.

Investigations continued

- Investigate the following areas:
  - Personnel,
  - Materials,
  - Equipment,
  - Process/Methods,
  - Suppliers,
  - Validation,
  - Storage conditions,
- Think big, think creatively.

Investigations continued

Document all investigation activities.

- At a minimum, include the following elements:
  - Description of Nonconformity Event
  - Root or Probable Cause
  - Outcomes of all tools used
  - Objective evidence supporting conclusions
  - Description of statistical methods used
  - Final risk assessment

Investigative Tools

- Brainstorming
- Fishbone
- 5 Whys
- Design of Experiments
- Contradiction Analysis

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Resolutions

- Corrections
- Interim Modes of Control
- Corrective Actions
- Preventive Action

Correction

- Correction: Action taken to fix a detected nonconformity.
  - Typically one time fixes.
  - Immediate solution such as training, repair or rework.
  - Also known as remedial or containment action.
- Corrections require verification.
- Thorough documentation required

Correction, continued

- Interim controls
  - Type of correction that remains in place until a corrective action is deemed effective

- Examples
  - 100% inspection
  - Third party oversight and review

Corrective Action

- Corrective action (CA): action to eliminate the cause(s) of a detected nonconformity or other undesirable situation and the recurrence of the issue.

Corrective Action continued

- Write a Corrective Action Plan.
  - Identify the CA strategy.
  - Describe all the corrective actions that will be performed and associated action items.
  - How will the corrective action be tested
  - Identify who is responsible for each action item.
  - Set a timeline with completion dates.

Corrective Action continued

- Implement the Corrective Action(s).
- Implementation requires monitoring and oversight.
  - Structured monitoring of progress against actions, monitoring of the impact of actions, engagement of management, and governance.
  - Documents any changes, and reflects any revisions or changes to timelines in the documentation.
  - Formal tracking of the overall progress of the CA, tracking of the individual actions, and review of milestones on a defined frequency.

Preventive Action

- Preventive Action (PA): action to eliminate the cause of a potential nonconformity or other undesirable potential situation. Should prevent the occurrence of the potential issue.
- Not dependent on the occurrence of a nonconformity
- Example: Results of a Finished Product QC check are within specification limits yet over the past 10 batches are trending upward.

Preventive Action continued

- Preventive action require a plan with same elements as a corrective action:
  - Write a plan.
  - Implement the preventive actions.
  - Monitor preventive action activities.

Effectiveness Check

Effectiveness Check (EC): Monitoring activity over a defined duration for ensuring that

- CA/PA's have been identified, implemented, and sustained
- the problem has been solved, and
- no new quality problems have been created.

Effectiveness Check continued

- Key Components of Effectiveness Checks:
  - Methods for determining success of the Corrective Action or Preventive Action must be defined.
  - Effectiveness criteria or key performance indicators must be measurable.
  - Duration for conducting effectiveness checks must determined.
  - Data, graphs, charts, metrics as applicable for evidence of effectiveness of the Corrective or Preventive Action

Effectiveness Check continued

Effectiveness Check Plan:

- Addresses the key elements.
- Describes statistical techniques to be used.
- Lists responsibilities and includes due dates.

CAPA Closure

- All actions must be completed and assessed for effectiveness prior to CAPA closure.

  (Note: In rare occasions CAPA may be closed prior to effectiveness check however solid justification is required.)

- Use common sense

Corrective Action/Preventive Action

- Not all nonconformities require Corrective or Preventive Action.

- If Corrective or Preventive Action are not necessary, as determined by Quality, then appropriate justifications should be documented and approved.

Corrective Action/Preventive Action continued

- Low Level Investigations may not routinely require CAPAs.
- However, these investigations should be tracked and trended.
- If a recurring trend is found, Corrective Actions should be required.

Corrective Action/Preventive Action continued

CAPA Leader

- Excellent communication/presentation skills.
- Strong analytical problem solving skills.
- Influence management skills; ability to work constructively across all functions of the organization.
- Experience in all areas of the CAPA process.
- Experience with quality tools and process improvement techniques.
- Project management experience.

Timeliness

Timeliness

- Not completing/closing CAPAs in a reasonable time is a red flag to an investigator.
- Not all CAPA are equal; some CAPAs can be closed in few months others will take several months.
- Measure the CAPA process for timeliness.
- Take action when CAPAs are not progressing per plan.

Timeliness – Red Flags

- Open over a year.
- No progress for 3 months.
- Not getting to root cause in 3 to 6 months.
- Corrective action(s) taking more than 6 months.

Timeliness – All CAPAs are not Equal

- CAPAs using simple investigation tools may get to root cause faster than using complex tools.
- Corrective actions which requires a new or revised procedure will take less time than ones requiring a new design or equipment change.
- Key – set completion expectations based on the complexity of the CAPA.

Timeliness - Metrics

- If you can't measure it, it will not improve.
- Determine metrics to drive the correct behavior and review monthly.
- Possible metrics:
  - Number of days to get to root cause.
  - Number of days to complete a corrective action.
  - Number of days to close a CAPA.
  - Percentage of CAPAs closed per plan
- Set goals for each and revise as process improves.

Timeliness – Take Action

- Review metrics monthly with your CAPA team.
- Determine how many months above goal before taking action.
- Take corrective action to get metrics back on track.
- Established when to escalate issues to management

Tracking and Trending

- Establish requirement for opening a CAPA based on risk of impact and frequency of the noncompliances.
- Need to track and trend corrected noncompliances that do not meet requirements for opening a CAPAs.
- Track and trend within the data sources.

Management Review

- Use Management Review to inform management the effectiveness of your CAPA system.
- Select the key critical metric(s) used to drive correct behavior. Possible metrics:
  - Number of days CAPAS are open.
  - Percentages of CAPAs closed on time.
- Document any actions taken.

When to Create a CAPA

- Not all nonconformance needs to become a CAPA.
- Use a method to determine if a CAPA is needed.
- Use a combination impact and frequency.

Frequency \ Impact	Little	Minor	Major	Critical
Rarely	L	L	M	M
Occasionally	L	M	M	H
Frequent	L	M	H	H
consistent	M	H	H	H