Writing (and ensuring) Good Failure Investigations and CAPA Reports

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“Writing is thinking on paper.”

William Zinsser
Critical Thinking


1. What are the **issue** and the **conclusion**?
2. What are the **reasons**?
3. Which words or phrases are **ambiguous**?
4. What are the **value conflicts** and **assumptions** (descriptive or otherwise)?
5. Are there any **fallacies** in the reasoning?
6. How good is the **evidence**?
7. Are there **rival causes**?
8. Are the **statistics deceptive**?
9. What **significant information** is **omitted**?
10. What **reasonable conclusions** are possible?
Challenges

- Senior management support
- Sufficient, knowledgeable staffing
- Faster pace, tighter deadlines, increased workload
- Increasing regulatory requirements
- Globalization
- Increasingly sophisticated products and software
- Working with others, training and coaching, communication

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Environment

Source: Eyes Wide Open: How to make smart decisions in a confusing world, Noreena Hertz

• 75% of our waking time is spent receiving information
• Email is the number one enemy
• Data deluge, feel driven to answer calls, continually check email, check voice mail, respond immediately
• Stress, distraction, unpredictable events, uncertainty
• Do not often check-in with our feelings and understand how exhausted we are
• What to believe? What to reject? Finding intelligence among all the noise.
Good Decision Making

Source: Eyes Wide Open: How to make smart decisions in a confusing world, Noreena Hertz

• Think about own thinking process.
• Take more control of decisions and how to make them.
• Ask for help when needed.
• Choose individuals who have the skill set(s) you need.
• Look into your own psyche; identify ways you may be sabotaging your own decision making.
Suggestions

Source: Eyes Wide Open: How to make smart decisions in a confusing world, Noreena Hertz

• Seek different opinions.
• Challenge experts.
• Ensure everyone has a voice, not only technical experts or high-ranking individuals.
• Become comfortable with nuance, uncertainty, doubt.
• Work with experts to help figure things out, but be aware of their limitations and our own.
Medical Device CGMPs

Medical Device CGMPs, 21 CFR 820.100, Corrective and Preventive Action

- Each manufacturer must establish procedures for implementing corrective and preventive action, including requirements for:
  - Analyzing quality data sources to identify existing and potential causes of nonconforming product
  - Investigating cause of nonconformities relating to product, processes, and the quality system
  - Identifying action needed to correct and prevent recurrence of nonconforming product and other quality problems
  - Verifying or validating corrective and preventive action
  - Implementing and recording changes in methods and procedures
  - Ensuring information related to quality problems or nonconforming product disseminated to those responsible, including identified quality problems and corrective and preventive actions, for management review
- All activities and their results shall be documented.

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CAPA Starburst

Potential data sources for a CGMP Corrective and Preventive Action Program
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Drug cGMPs
Source: 21 CFR 211.192, Production Record Review

- All drug product production and control records shall be reviewed and approved by quality control unit to determine compliance with all procedures before a batch is released or distributed.

- Any unexplained discrepancy (including percentage of theoretical yield exceeding maximum or minimum percentages established in master production and control records) or 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.

- Investigation shall extend to other batches of 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.

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API CGMPs
Source: ICH Q7A, 2.2, Responsibilities of the Quality Unit(s)

• Main responsibilities of independent quality unit(s) shall not be delegated. These responsibilities should be described in writing and shall include:...

• 4. Making sure critical deviations are investigated and resolved....

• 11. Making sure quality-related complaints are investigated and resolved

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Human Cells, Tissues, Cellular and Tissue-Based Products (21 CFR 1271)

Source: 21 CFR 1271.160 (3) and (6); 21 CFR 1271.195 4 (b)

• Establishment and maintenance of a quality program
  – Ensure appropriate corrective actions including reaudits of deficiencies are taken and documented
  – Verify corrective actions to ensure actions are effective and in compliance with CGTP.
  – Corrective actions must include both short-term action to address immediate problem and long-term action to prevent problem’s recurrence.
  – Thoroughly document corrective actions.

• Environmental control and monitoring
  – You must take appropriate corrective action as necessary

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Good Laboratory Practices


• Testing facility management
  • ...assure any deviations from regulations reported by QAU communicated to study director and corrective actions taken and documented

• Study director
  • ...unforeseen circumstances that may affect quality and integrity of study noted when they occur and corrective action taken and documented

• Quality assurance unit
  • ...inspect each study...any problems found during course of inspection which affect study integrity shall be immediately brought to attention of study director and management
  • ...determine that no deviations from approved protocols or SOPs made without proper authorization and documentation.

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Top 483 Observations: Drugs
FY 2012 data, www.fda.gov

• Procedures not in writing, fully followed
• Investigations of discrepancies, failures
• Absence of written procedures
• Scientifically sound laboratory controls
• Control procedures to monitor and validate performance
• Written procedures not established, followed
• Calibration/inspection/checking not done
• Training: operations, GMPs, written procedures
• Cleaning/sanitizing/maintenance
• SOPs not followed/documented
• Testing and release for distribution
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Top 483 Observations: Devices
FY 2012 data, www.fda.gov

- Lack of or inadequate procedures
- Lack of or inadequate complaint procedures
- Lack of written MDR procedures
- Purchasing controls: lack of or inadequate procedures
- Documentation (CAPA)
- Nonconforming product control procedures
- Lack of or inadequate process validation
- Design changes: lack of or inadequate procedures
- Investigation of device failures (complaints)
- Quality audits: lack of or inadequate procedures
Top Clinical 483 Observations
FY 2012 data, www.fda.gov

- FD-1572, protocol compliance
- Inadequate case history records, including informed consent and data
- Minutes of IRB Meetings
- Accountability records
- Initial and continuing reviews by IRBs
- Consent form not approved/signed/Dated
- List of members of IRBs
- General responsibilities of sponsors
- Problems not reported to IRB
- Informed consent
Key Points

• Patient safety should always be our #1 concern.
• The depth and intensity of any investigation should match the possible risk to the patient.
• When in doubt, it is better to conduct an investigation.
• The final decision on whether to investigate should be made by an experienced QA professional.

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Terms

Source: GHTF Proposed Document, Quality management system – Medical Devices -- Guidance on corrective action and preventive action and related QMS processes

• **Correction**
  – Action to eliminate a detected nonconformity

• **Corrective action**
  – Action to eliminate the cause of a detected nonconformity or other undesirable situation
  – Corrective actions must encompass the need to correct the nonconformity and in addition address systemic problems

• **Preventive action**
  – Action to eliminate the cause of a potential nonconformity or other undesirable situation
  – By its very nature preventive action can not follow a nonconformity

• **Nonconformity**
  – Non fulfillment of a requirement

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Timeliness
Source: The Barr Decision

• Problem investigations should be done in such a way to correct existing problems and to prevent related future problems.

• Problem investigations should be completed in a timely manner not to exceed 30 days from discovery of problem, unless additional time is required for activities such as stability studies or regulatory submissions.

• All problems implicating a distributed batch or ability to supply acceptable batches shall be investigated with utmost urgency.

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Problem Investigation Toolkit
22 Great Investigation Tools

• 1. Notify your supervisor or QA promptly (within 24 hours).
• 2. Draft a clear, complete problem definition.
• 3. Assess patient safety and product impact.
• 4. Use your company’s forms/SOPs, and fill forms out completely.
• 5. Describe immediate corrective action(s) taken.

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Problem Investigation Toolkit
22 Great Investigation Tools

• 6. List all possible causes.
• 7. Create a timeline or chronology.
• 8. Look for any prior occurrences.
• 9. Look for any changes or differences.
• 10. Look for the “ripple effect.”
• 11. Brainstorm root causes.
• 12. Create an investigation plan.

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13. Carry out the investigation; most should be done within 30 days.


15. Analyze the information.

16. Brainstorm and select best possible solutions; apply your criteria.

17. Create an action plan.
Problem Investigation Toolkit
22 Great Investigation Tools

• 18. Follow up.
• 19. Document well; use the inverted pyramid writing style.
• 20. Measure CAPA effectiveness.
• 21. Get the investigation approved.
• 22. Communicate the results to everyone involved, including other sites.

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Determine Root Cause

Source: Dean Gano, Apollo Root Cause Analysis: A New Way of Thinking

- Working with a group of peers, brainstorm possible root causes for major or more critical problems
- Always look for *at least two* causes in form of pre-existing conditions and actions (catalysts)
- Effort should extend beyond effects of problem to discover its most fundamental cause(s)
- Prepare investigation plan

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Root Cause Analysis

Select The Best Solutions
Source: Dean Gano, Apollo Root Cause Analysis: A New Way of Thinking

• Working from confirmed causes, brainstorm possible solutions. Try not to go for quick fix (retrain operator).

• Apply criteria to select best solution:
  – Solution that prevents recurrence of problem, including at other locations
  – Solution that does not cause unacceptable problems
  – Solution is within your organization’s control
  – Solution that provides good value for its cost
Close the Loop

- Management with executive responsibility must be aware of and review CAPA results. Organization must take prompt action when violative products or situations are discovered.
- A surveillance system is only as good as the information it receives; we must be able to rapidly pick up on important signals.
- Follow up is crucial. Close loop by providing input into design control/R&D requirements/study design.
- Nonconforming product identified and corrected before distribution.
Assessing Potential Risk

• Decision should be made by properly qualified/trained staff.
• Risk to patient should be supported by documented risk assessment. Clinical or medical staff may need to be consulted.
• Whether to pursue problem investigation or corrective action based on magnitude of problem and any related risk.
• Determination of risk, rationale for no investigation or CAPA (if warranted), and criteria used should be documented.

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Required Notifications (Partial List)

- Procedures for:
  - Medical Device Reports (21 CFR 803)
  - Biological Product Deviation Reports (21 CFR 600)
  - Field Alerts (21 CFR 314)
  - Adverse Event Reports (21 CFR 310, 314, 600)
  - Recalls (21 CFR 7)
  - Corrections and Removals (21 CFR 806)

- Ensure timely and effective identification, communication, and investigation of events that may require FDA notification.
Investigation Management (1 of 2)

Source: Daniel S. McDevitt, Managing the Investigative Unit

• Case Screening
  – Which cases should be assigned for follow-up investigation

• Case Assignment
  – Aptitude of investigator
  – Complexity of investigation
  – Special interests of investigator

• Case Reporting
  – Set format to ensure complete package
  – Finished package is organized and clear
  – Listing of evidence, root causes, individuals interviewed, table of contents, reports and documents

• Filing System
  – Complete – all investigation documents included
  – Easy to understand
  – Secure
• Investigation Planning
  – Tasks, timetable
  – Review initial report
  – Require written investigation plan, logical detail, for new investigators, or individuals whose performance may be less than stellar

• Case Review
  – Ongoing, not single event
  – Confirm work being done
  – Ensure currency of reporting
  – Keeps you abreast of priorities
  – Aids in proper expenditure of resources
  – Identifies training needs
  – Regularly scheduled review
Desirable Qualities for Investigators

Source: Managing the Investigative Unit by Daniel S. McDevitt

• Success often depends on verbal communication skills and is affected by display of genuine sensitivity and concern throughout interviewing and information gathering process.
• Do listeners willingly provide information to them? Are they comfortable interviewing line personnel, supervisory personnel, and executives?
• Is individual capable of preparing professional reports? They must be legible, concise, accurate, comprehensible, and complete.
• Can the individual successfully interact with people without repeatedly being conned?
• Do they have stamina? Are they willing to work long hours?
• What is quality of their work?
• What is their work behavior? Do they demonstrate motivation, stability, “street” knowledge, persistence, intelligence, judgment, teamwork, reliability, and dedication?
• Are they punctual, do they have professional appearance and demeanor, good verbal communication skills, and the ability to follow directions?

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Interviewing Tips
Source: The Art of the Interview by Martin Perlich

• Interview: *mutual* process in which skilled practitioner extracts through conversation data from an individual which will be *useful* and *interesting*. There are only two rules:
  – 1. Prepare
  – 2. Listen
• Be attentive, display highest level of sensitivity, make a connection.
• Always assume your first question may be your last. Make it count.
• Listen to their response. Did he/she pause before answering? Was response what you expected? Closely observe body language, voice tone, other intuitive data. If answer stingy, incomplete or inadequate, try saying nothing and looking intently at them as if you’re too polite to interrupt.
• Don’t be intimidated by reputation or personal regard. They may be more nervous talking to you than you are about talking to them.
Training Topics
Source: Daniel S. McDevitt, Managing the Investigative Unit

- Emphasize high-frequency tasks they will be expected to do daily, such as:
  - Investigation techniques and planning; root cause analysis
  - Your investigation and CAPA SOPs, and computerized/filing system
  - Applicable regulations and standards, applicable guidance
  - Report writing. New investigators are moving from simple report format to pure narrative format.
  - Interview techniques. Some line personnel have limited experience participating in a lengthy interview.
Span of Control
Source: Daniel S. McDevitt, Managing the Investigative Unit

• For an investigative unit, normal span of control is 5-7 investigators per supervisor.
• Also consider geographic region covered and complexity of assignments covered.
• If a large geographic area is covered, and many specialties are covered, the quality of management will suffer.

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Writing Tips

• Include an executive summary at front of reports – with all critical information and clear recommendations.
• Write in inverted pyramid style, with most critical information in first two to three sentences.
• Write a clear and complete problem description that would be intelligible to someone from outside your organization.
• Use tables to provide detailed information. Put source of the data near or around table. Double-check all data presented.
• Spell out all acronyms on first usage.
• Group all related information under a subheading.
• Use bulleted points and “white space.”
• Read the report aloud to catch any errors your eyes may miss.
• Number and title any attachments.
• If time allows, draft the report, put it aside for at least one day, and edit it. Discuss all areas investigated, even if they were a “dead end.”
• Write reports for members of your organization, not for FDA.
Inverted Pyramid Writing Style


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Draft a clear, complete problem definition.

• Define problem as thoroughly as possible in technical terms as well as in terms of effect on product quality and availability.

• *Success of later steps depends upon how well this first one is done.*

• Determine extent or scope (in terms of batches, products, time period, and processes).

• SOP should outline steps needed to determine whether investigation should extend to other lots, dosage strengths, dosage forms, or products.

• Review and determine safety, quality, technical, regulatory compliance, and product supply implications.

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Speaker’s (Writer’s) Questionnaire

Source: The Buckley School of Public Speaking

• Answer these questions to help you prepare any presentation or writing assignment:
  • What are you trying to accomplish?
    – What do you want to tell your audience?
    – What do you want your audience to do?
  • Key Messages (Nut Graph): What do you want them to remember?
    • A.
    • B.
    • C.
• Personal Goals: How do you wish to be perceived?
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How Readers Approach Reports

Source: Guide to Report Writing, Michael Netzley and Craig Snow

• Readers are task-oriented.
• They read reports to understand and act on the information.
• Reports are not leisure reading.
• An effective report is not a random collection of data, not a mind dump, nor an opinion piece.
• Effective report is well-structured message designed to be read quickly and help readers understand and act on information.
• Reports are tools helping people make informed decisions.
• Effective reports are timely. They arrive when promised and present current information.

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What Makes Reports Effective?

Source: Guide to Report Writing, Michael Netzley and Craig Snow

• Reports are chief vehicle by which organizations communicate authoritative, substantive, and reliable news or information.

• Reports are among most important messages you prepare at work.

• Quality of your reports will influence your professional success. They depict your competence: how well you think, how well you gather, assemble, and analyze data, how well you draw conclusions and recommendations from data, how well you support your assertions, and how well you create messages that meet the needs of your readers. Your credibility is on the line every time you prepare a report.
Meet Needs of Key Readers

Source: Guide to Report Writing, Michael Netzley and Craig Snow

• Identify key audience. Make informed choices re: topics, level of detail, and report structure – enabling readers to use each report.
  – Who will read the report and use information it contains?
  – How will they use the information? What specific decisions will they make based on data, conclusions, and recommendations?
  – What specifically should you address in report so you can be confident you enable readers to use the report as they see fit?
  – What specifically might you do in report to meet – and if possible exceed -- your readers’ expectations?
  
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Resources (1 of 2)

• All applicable regulations and preambles; all applicable ICH, GHTF, and FDA guidance documents; all applicable standards (ISO)
• ISO 13485:2003, Medical devices – Quality management systems, Requirements for regulatory purposes (terms)
Resources (2 of 2)

- FDA Inspection Observations, [http://www.fda.gov/ICECI/EnforcementActions/ucm250720.htm](http://www.fda.gov/ICECI/EnforcementActions/ucm250720.htm)
- FDA ORA FOIA Reading Room, [http://www.fda.gov/AboutFDA/CentersOffices/ORA/ORAElectronicReadingRoom/default.htm](http://www.fda.gov/AboutFDA/CentersOffices/ORA/ORAElectronicReadingRoom/default.htm)
- Managing the Investigative Unit, Daniel S. McDevitt
- Guide to Report Writing, Michael Netzley and Craig Snow
- The Reid Technique, Interviewing and Interrogation, John E. Reid & Associates (CD/videotape)
Questions?

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