Effective Investigations and Corrective Actions (CAPA)

Proper Investigation of Quality Events

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What Do You Do When The Bad Stuff Happens?

Ignore It  Pretend It Never Happened
Advise Boss  Curse
Walk Away  Advise Your Buddy
Fix It  Investigate + Fix
Blame Someone Else  Investigate
Investigate, Fix + Document
Failure/Deviation System

The purpose of a failure/deviation system is to assure that each failure/deviation does not adversely impact product quality and that effective corrective action is taken to reduce the probability of such failure in the future.

Why Should We Investigate Failure?

but why investigate?

It makes good business sense.
Contributors to Failure

- Materials
- Facilities
- Equipment
- Instrumentation
- People
- Processes
- Procedures

Failure / Deviation

**Definition**

**Failure**
- Product does not meet specification.
- Failure may be detected in/by
  - Production
  - Laboratory

**Deviation**
- Change in procedures, equipment, materials, personnel related to product manufacture having an impact on product quality
Definitions

- **Immediate Cause**
  Situation directly causing the problem

- **Root Cause**
  Basic Causal Factor, which if corrected or removed prevents a repeat of the problem

- **Intermediate Cause**
  Reason for problem at more fundamental level than the immediate cause, but not the root cause \[why-2, why-3\]

- **Root Cause Analysis**
  Structured questioning process enabling identification of underlying beliefs and practices that result in poor quality

Causes of Failure

**Common Cause \[Endemic - Systematic\] (Variation)**

Originates from the basic elements of the process:
- Machines
- Materials
- Methods
- Manpower
- Measurement

**Assignable Cause \[Special\] (Variation)**

An unplanned variation originating outside expected operating process conditions \[special cause variation\]
Failure/Deviations Measures

There are three key steps in this process and each of these should be monitored regularly:

- **Recording the failures and deviations**
  - Total number
  - Number by department

- **Action on product batch(es) involved**
  - Audit by sampling to verify that corrective action was taken

- **Corrective action on root causes**
  - There should be an elimination of failures/deviations due to causes for which corrective actions have been implemented

Regulators Expectations

- **Comprehensive, Honest Approach To Investigate OOS Results/Failures**
- **Evaluation Using Scientifically Valid Principles**
- **Learning From Experiences**
- **Permanent Solutions To Problem**
- **Authorities Not The Ones To Find The Problem**
b) Numerous lots of Thymoglobin did not meet specifications for capping defects during filling and capping operations for which you are the contract manufacturer. Nevertheless, the quality control unit did not thoroughly investigate these defects.

c) The quality control unit did not ensure that the particulates in lots of Haemophilus b Conjugate Vaccine were thoroughly investigated. The investigation was limited to the laboratory and did not include input from other departments, including manufacturing, to determine whether particulates were coming from another source.

d) Review of batch production records for lots 200480-2 and W1366-2 was not adequate because the quality control unit did not identify label accountability errors and the errors. These errors were not investigated.

e) The quality control unit does not ensure that environmental monitoring excursions are thoroughly investigated. For example, the investigations for class [redacted] area environmental monitoring excursions did not include the identification of the organism for nonperformance investigations 2003-05499 and 2003-005099.

f) The quality control unit does not ensure that WFI excursions for some areas are thoroughly investigated. Examples include the microbial excursions of too numerous to count organisms on post [redacted] in [redacted] in April 2002, and the action level excursions for total organic carbon (TOC) in [redacted] in September 2003 and February 2004.
What Do The US Regulations Say?

"Investigation" specifically stated in the cGMPs:

- §211.22 - Responsibilities of quality control unit.
- §211.125 - Labeling issuance.
- §211.170 - Reserve samples.
- §211.180 - General requirements.
- §211.186 - Master production and control records.
- §211.188 - Batch production and control records.
- §211.192 - Production record review.
- §211.198 - Complaint files.
- §211.204 - Returned drug products.
What Does The EU Guide Say?

“Investigation” specifically stated in the GMPs:

- 1.3 Quality Assurance
- 1.4 Quality Control
- 2.7 Production/QC Responsibilities
- 5.39 Production
- 5.56 Packaging Operations
- 6.2 Quality Control
- 8.1 Complaints

Future Regulations

An international harmonized approach to

Risk Management

ICH-Q9
ICH-Q9
Risk Management

Risk management tools

- risk assessment
  - risk identification
  - risk analysis
  - risk evaluation

- risk control
  - risk reduction
  - risk acceptance

- risk communication
  - output/results of the risk management process

OK → risk acceptance
unacceptable → review event

CAPA
CAPA

How do you know what’s happening?

Recognize that there is a problem:
- Capture The Data
- Analyze The Data
- Trend The Data

Then Fix the problem:
- Investigate the Cause
- Attempt to Get to “Root Cause”
- Implement Effective Fixes
- Monitor the Fix

fixing ain’t good enough
you have to prevent it happening again
§820.100 Corrective and preventive action

(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.
CAPA – Analyzing Sources of Quality Data

Complaints/Returns

Repairs/Servicing

Calibration/Maintenance

Environmental Monitoring

Process Deviations or Failures

Acceptance Activities

Stability Data

Audits

Yields/Scrap

What To Track

Track By:
- Product: In-process, release, stability, validation
- Event: Reason for investigation
- Operator/Analyst: If cause is operator/analyst error
- Instrument/Equipment: If cause instrument related
- Cause: Investigation conclusion
- Corrective Action: Remedy and prevention
- Timeliness: Time to complete investigations
CAPA Data Collection

Incidences Reported - 2003

Question:
Are we Getting Better as a Company?
Or Dropping Off in Capturing Incidents?

Run Charts: Trend Charts
Environmental Data - Purified Water System
Tracking / Trending

- Paper/Pen
- Spreadsheet (Excel, Oracle)
- Dedicated Computer Systems
  - Trackwise
    - (Sparta Systems: http://www.sparta-systems.com)
  - CATSweb
  - MetricStream
    - (Metric Stream: http://www.metricstream.com)
  - SmartCAPA
    - (SmartCAPA: http://www.pilgrimsoftware.com)
  - Others .....
Purpose of Investigation

The purpose of an investigation is to determine the cause of the failure.

Even if the batch is rejected based on the OOS result, the investigation is necessary to determine if the result is associated with other batches of the same drug product or other products.

FDA: Draft OOS Guideline, September 1998
Failure / Deviation - What To Do

1. Failure/Deviation Detected
2. Perform Investigation
3. Root Cause Analysis
4. Communicate to Management
5. Corrective/Preventive Action
6. Assess Effectiveness of Fix
7. Inform QA
8. Batch Disposition
9. Immediate Fix

- 24 hours
- 30 days

Investigations: You've Got to Be A Detective!
Investigations 101

Purpose of an Investigation
Obtain facts as to cause
- Common
- Special - Assignable

Process of an Investigation
- Complete description of problem
- Validity of inputs
- Review key process variables
- Determine scope of investigation
- Document investigation

Learn How To Be A Detective

What Equipment, Machine, Tool?
What is Wrong?
What Is the Complaint?
What is the Undesired Behavior?
Learn How To Be A Detective

Who is Involved?
- Staff
- Consultants
- Vendors
- Visitors

Name names/positions!

When does the problem occur?
- Day
- Date
- Time
- Shift
- Phase of operation
- When in equipment life cycle

Are there time patterns?
Learn How To Be A Detective

**Where?**

- Unit
- Area
- Department
- Line
- Machine

Location of defective item, or where on defective item

Learn How To Be A Detective

**How?**

How is the “what” or “who” impacted?
- Injury / Death
- Shut-Down /Start-Up
- Damage
- Type
- Classification of Defects

How Much
How Many
How Big An Issue
- What resources are needed to handle/resolve the issue!
**Change Analysis**

<table>
<thead>
<tr>
<th>WHAT?</th>
<th>COMPARISON?</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is the object or</td>
<td>What similar object or process doesn't have the problem? What else could be wrong?</td>
</tr>
<tr>
<td>process with the</td>
<td></td>
</tr>
<tr>
<td>problem?</td>
<td></td>
</tr>
<tr>
<td>What is wrong?</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>WHERE?</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Where does the problem</td>
<td>Where else could the problem occur?</td>
</tr>
<tr>
<td>occur?</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>WHEN?</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>When did the problem</td>
<td>When did the problem not happen?</td>
</tr>
<tr>
<td>happen?</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HOW BIG?</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>How large is the problem?</td>
<td>How large could it be?</td>
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</tbody>
</table>

**Investigation Documentation**

*investigation report must tell the entire story, from beginning to end - it must stand alone!*

A ➔ B ➔ C ➔ D ➔ E
Investigation Documentation

- Date problem occurred
- Statement of the Problem
- Listing of batches impacted
- List of personnel interviewed
- Statement of each person’s opinions and memory of event
- Discussion of potential causes
- Discussion of potential impact
- Discussion of extent of problem
- Recommendations for fixes
- Statement of actions taken to fix
- Final decisions regarding batch
- Management approvals

Root Cause Analysis
Corrective actions to observations (usually symptoms) have limited effect on sustained improvement or elimination of recurrence of the failure.

Corrective actions need to address the underlying causes and root causes of a problem in order to eliminate the situation from recurring.

<table>
<thead>
<tr>
<th>Root Cause Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Equipment</strong></td>
</tr>
<tr>
<td>Design, Capability</td>
</tr>
<tr>
<td>Maintenance</td>
</tr>
<tr>
<td>Operator Error</td>
</tr>
<tr>
<td><strong>Procedures</strong></td>
</tr>
<tr>
<td>No Procedure</td>
</tr>
<tr>
<td>Wrong Procedure Used</td>
</tr>
<tr>
<td>Procedure Not Available</td>
</tr>
<tr>
<td>Procedure Difficult To Use</td>
</tr>
<tr>
<td><strong>Training</strong></td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>When</td>
</tr>
<tr>
<td>Effectiveness</td>
</tr>
<tr>
<td><strong>Quality Control</strong></td>
</tr>
<tr>
<td>Inspection Required</td>
</tr>
<tr>
<td>Inspection Performed</td>
</tr>
<tr>
<td><strong>Management Systems</strong></td>
</tr>
<tr>
<td>Qualified Supervision</td>
</tr>
<tr>
<td>Audits</td>
</tr>
<tr>
<td>Feedback</td>
</tr>
<tr>
<td>Prior Corrective Actions Taken</td>
</tr>
<tr>
<td>Communication</td>
</tr>
<tr>
<td>Planning</td>
</tr>
<tr>
<td>Process Capability</td>
</tr>
<tr>
<td>Adequate Time To Perform Task</td>
</tr>
<tr>
<td>Standards</td>
</tr>
<tr>
<td><strong>Manpower</strong></td>
</tr>
<tr>
<td>Information Available</td>
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<tr>
<td>Adequate</td>
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<tr>
<td>Timely</td>
</tr>
<tr>
<td>Personnel Problems</td>
</tr>
<tr>
<td>Training</td>
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<tr>
<td>Fail-Safe Processes</td>
</tr>
<tr>
<td>Environment</td>
</tr>
<tr>
<td>Lighting</td>
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<tr>
<td>Noise</td>
</tr>
<tr>
<td>Fatigue</td>
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</tbody>
</table>
Corrective Action

What is the lowest level at which we can do something to prevent the problem from re-occurring?

Tools To Investigate
Investigation Tools

- Brainstorm the issues
- Flowcharting
- Fishbone Analysis - Cause/Effect diagrams
- Why-Why Analysis
- Pareto Charts
- Run Charts
- Force Field Analysis
- Six-Sigma Analysis - MAIC
- Kepner-Tregoe®

Brainstorming

Possible target questions to serve as the focal point of the brainstorming process:

- What would solve the problem?
- What strategy could resolve the root cause?
- What solutions have already been thought of?
- What solutions have not been thought of?
- How can we prevent the situation recurring?
- What different methods might work?
- What crazy ideas might help?
Fishbone Analysis

- Manpower
  - People too busy
  - People not paying attention
- Management
- Batch Record Errors
- Methods
- Machines

Why-Why Analysis

- Why
- Why
- Why
- Why
- Why
Pareto Analysis

Pareto: 80 – 20 rule

Batch Record Problems

Process Shift, F-440 Particle Size
APR – Annual Product Review

Digoxine Tabs - Dissolution

Xbar chart

Range chart

1/2000, 06/04/30: UCL=84.0, Mean=86.6, UCL=84.0 (12/2000, 06/04/30) (n=2)

Last 100 Batches

Force-Field Analysis

The Positive/Negative Analysis for Solutions can stimulate thinking just as the force-field format did in the past. Since we are looking for solutions, the two columns play “better” against “worse”.

<table>
<thead>
<tr>
<th>What would make the problem better?</th>
<th>What would make the problem worse?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>1.</td>
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<td>2.</td>
<td>2.</td>
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<td>3.</td>
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<td>4.</td>
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<td>5.</td>
<td>5.</td>
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<td>6.</td>
<td>6.</td>
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<td>7.</td>
<td>7.</td>
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<tr>
<td>8.</td>
<td>8.</td>
</tr>
</tbody>
</table>
**Six Sigma Problem Solving – MAIC**

**Measure**

1. Describe the Problem
   - What
   - Where
   - When
   - Extent

2. Determine When Problem Started

3. Measure Problem Magnitude

**Analyze**

4. Identify Potential Causes

5. Analyze Existing Data

6. Construct List of Verified Facts

7. Compare Causes to Facts

**Improve**

9. Determine Best Solution

10. Pilot Solution

11. Verify Solution Works

**Control**

12. Implement Solution

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**FACTS**

- All Machines
- Second Shift
- Certain Codes
- Started 8/22
- Steadily Worse
- All Operators

**Tools To Effect Fixes**
**Tools To Prioritize**
**Fixes and Efforts**

- **FMEA** - Failure Mode Effect Analysis
- **FTA** - Fault Tree Analysis
- **HACCP** - Hazard Analysis, Critical Control Points
Bibliography

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- Kepner and Tregoe, "The New Rational Manager"
- Paradies and Unger, "Taproot: The System for Root Cause Analysis, Problem Investigation & Proactive Improvement"
- Ammerman, "The Root Cause Analysis Handbook"
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- Harbour and Kieffer, "Managing the Quality System"

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- "Investigating Out of Specification (OOS) Test Results for Pharmaceutical Production" (Guidance), September 1998
- Quality Systems Approach to Pharmaceutical GMPs, September 2004

Stay In Touch

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T H A N K Y O U!

Questions?