Need for Proper Investigations

Inadequate investigations remain one of industry’s top five inspectional findings by FDA in domestic and foreign pharmaceutical company inspections.

Consistent with inspectional findings from many other health authorities around the world.

Examples:

- Lack of adequate detail
- Scope not broad enough
- Inadequate rationale for batch disposition
- Lack of root cause analysis
- Failure to address issues at CMOs
- Complaints not substantially investigated or trends not detected

Presentation Overview

- Expectations of a Well-Executed Investigation
- Staffing and Scoping an Investigation
- Executing an Investigation
- Corporate Control and Vigilance
- Assuring Effectiveness of Corrective Actions
Investigation Expectations

FDA Expectations

Industry Views
- Compliance
- Corporate responsibility
- Financial benefit

Industry trends

Investigations: FDA Expectations and Findings

- Clearly the responsibility for maintaining quality rests squarely with the manufacturers themselves...the widespread and successful adoption of six sigma and related quality management techniques in other manufacturing sectors would imply that reliable, high-quality manufacturing is also attainable in the pharmaceutical sector.

- We must ask ourselves, in an area where the stakes are so high, why is this not being achieved?

Dr. Janet Woodcock, Commentary in May-June 2012 edition of PDA Journal

Richard L. Friedman, M.S. Associate Director, OMPQ, Office of Compliance, US FDA

PDA/FDA Improving Investigations Workshop, September 18, 2013

Preventing Adverse Quality Impact

Identity Signals
- Identify internal signal (QC/QA) before there is a drug quality consequence
- Monitor external (voice of customer) signals, especially complaints

Prevention
- Implement current process controls, robust statistical sampling plans, operational supervision, and recording of anomalies as deviations
- Such a quality culture will identify problems during process, before final QC stage

When a meaningful manufacturing issue is emerging/occurring
- Know when Management Escalation is needed to ensure timely communication
- Prevention/Correction may require obtaining resources for root cause determinations and reinvestment in facilities

Use the CAPA Program Effectively
- Catch leading indicators of quality problems internally and deal with them early, to avoid external failures (e.g., complaints, FARS/BPDR, recalls)
To Maintain a State of Control...

Science-based management of quality includes monitoring ongoing process control, and acting promptly to effectively address risks before the process falls out of a state of control.

Richard L. Friedman, M.S. Associate Director, OMPQ, Office of Compliance, US FDA
PDA / FDA Improving Investigations Workshop, September 18, 2013

Benefits and Elements of Establishing an Robust Investigation Process

The aim is to elevate compliance beyond execution to a strategic framework that integrates business processes with compliance requirements based on risk based solutions that are efficient, effective and innovative.

Juan L. Torres, PhD, SVP, Global Quality - Biogen Idec, PDA / FDA Improving Investigations Workshop, September 18, 2013

Process Improvement = Overall Benefit

Based on CEB large scale survey of over 850 employees across levels of seniority, functions, and industries to understand the nature and drivers of quality in a company’s culture.

Juan L. Torres, PhD, SVP, Global Quality - Biogen Idec, PDA / FDA Improving Investigations Workshop, September 18, 2013
Cost of Quality: models and the benefits

- Reducing the cost of poor quality is one of the best ways to increase a company's profit
- Provides management overview of quality
- Aligns quality and goals
- Helps prioritize problems and provides a means to measure process improvements
- Provides a means to distribute controllable quality costs
- Promotes effective use of resources
- Provides incentives for robust quality

Management Review and Responsibility for Investigations

Be proactive
- Address issues promptly
- Foster a continuous improvement environment
- Create management ownership
- Allocate resources adequately and appropriately
- Drive “Right the First Time” approaches
- Promote leadership and decision making across levels and functions
- Be persistent and tenacious

Standardized Root Cause Analysis (SRCA) Process Improves CAPAs

SRCA Process avoids “tunnel vision” by:
- Emphasizing that most events have multiple Causal Factors and Root Causes
- Requiring evaluation of Causal Factors and Root Causes
- Requiring confirmation of Causal Factors
- Evaluating each Causal Factor for Root Cause(s)
- Ensuring CAPAs are implemented for each identified Root Cause
Successful Investigations are Critical to the Health of Our Business

- Create a conducive environment for investigation execution
- Provide a robust investigation platform and corresponding support
- Build effective investigation teams with the appropriate ownership and participants
- Circular communication between management and investigation teams

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1. Q10 – Structure & Key Elements

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Engaging the Right People

**Subject Matter Experts**
- Method Development
- Microbiology
- Formulation Development
- Technical Operations
- Validation
- Supplier

**Investigation Team Leader**
- Site Quality Head
- Site Operations Head
- Global QA
- Global Technical Operations

**Management Sponsor**
- Matrixed organization
- Complex issues

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Key Staffing and Scoping Concepts

**Get management sponsorship!**

**Involving the right people is key**
- Get to Root Cause
- Timely closure
- Manage impact and communication

One size doesn’t fit all

Apply product, technology, supply chain and other external considerations when selecting a team

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Deviations, Complaints, QC Failures, and other Investigations

**How to Gauge Risk – Importance of Triage process**

- Complaints
- Product Rejections
- Non-Conformances
- Recalls
- Deviations
- Audits
- Regulatory Inspections and Findings
- Trends from Process Performance & Product Quality Monitoring

QRM and Knowledge Management serve as enablers to improve the efficiency and effectiveness of the Triage step and of the overall CAPA System.
QRM and KM to Assess Risks and Support Triage Process

Example Use of QRM to Develop a Control Strategy

Knowledge

Jacques Zimmowitch, Vice President Quality, Drug Product Operations, Americas and Asia - Eli Lilly and Company

PDA / FDA Improving Investigations Workshop, September 18, 2013

Presentation to PDA India Chapter © 2013 Parenteral Drug Association

Key concepts in this presentation

- Key Continuous Improvement Tools
- Ultimately Supports Operational Excellence

Investigations and CAPA

- Use Risk Assessment and Knowledge Management to focus resources and ensure Patient Safety

Triage

- Triage and investigate quickly, to control the problem, to collect and apply process knowledge and to escalate as required

Timing

- Control the impacted batches, but also consider what other products, materials, equipment or even other manufacturing sites could be impacted now or in the future

Scope

- Quality Impact
- Assessment
- Root cause
- Tools
- Quality Business Benefits

Executing an Investigation

Investigation Report
- Well-written
- Comprehensive

Quality Impact

Root Cause Analysis
- Tools
- Quality Business Benefits

Jacques Zimmowitch, Vice President Quality, Drug Product Operations, Americas and Asia - Eli Lilly and Company

PDA / FDA Improving Investigations Workshop, September 18, 2013

Presentation to PDA India Chapter © 2013 Parenteral Drug Association
Essential Components for a Thorough Investigation

- Are the right people and expertise at the evaluation/discussion table?
- Is the root cause(s) identified?
- Is the appropriate data complete and is it being reviewed?

Thomas Arista, National Expert Investigator - ORA FDA
PDA - FDA Improving Investigations Workshop, September 18, 2013

Notification Evaluation

- Is it major, minor or can it wait?
- Is this a deviation(s) and does it impact:
  - Due to product quality related complaints;
  - Issues related to non-sterile products;
  - Aseptic operations and/or due to media fill failures;
  - Microbial and/or non-viable particles contamination; and,
  - Are these reoccurring aberrant events?

Thomas Arista, National Expert Investigator - ORA FDA
PDA - FDA Improving Investigations Workshop, September 18, 2013

Essential Quality Unit Personnel

- Shop Floor Operations
  - Manufacturing/production
  - Engineering
  - I.T. staff
  - Maintenance
  - Laboratory Analysts
- First Line Supervisor/Team Leader
- Manager/Director
- Sr. VP/Ex. VP/VP
- Pres./CFO/COO
- CEO
Getting to the Root Cause

Risk is never zero • it is mitigated or reduced to an acceptable level.

Uncertainty is caused by having little or no data • beware of performing risk assessments with high uncertainty

Documentation and communication of risk is critical

Risk management and the associated tools • allow a sound decision to be made • not to justify it

Root Cause Analysis (RCA) Tools
Corporate Control and Vigilance

Investigation Input Triggers
- PPPQMS
- Management Review
- CAPA

Investigation Level
- Comprehensive
- Less intense

Corporate Control and Vigilance

Good Processes

Right People

Strong Systems

Permanent Inspection Readiness

Strong Compliance Culture

Benefits of Robust Proactive Compliance

Support and ownership of quality goes beyond quality/compliance units

Enhanced process stability drives productivity and performance

Prevention reduces compliance risks and costs

Fewer significant investigations and therefore, more efficient release of product

Protection of the product brand and reputation
Quality Lessons

Deviations occur/mistakes happen!

Key is to have systems in place that:

- Provide for strict accountability/checks and balances
- Investigate root causes
- Assure complete and systemic CAPAs
- Check effectiveness

Apply “Lessons Learned” across product lines, sites and throughout the organization

Lori F. Hirsch, Managing Counsel - Merck
PDA / FDA Improving Investigations Workshop, September 18, 2013

Handling Customer Complaints

Transition via a Phased Quality Strategy

GoAL
Quality Excellence

APPLICATION
Deployment of Defensive Process with Emphasis and Commitment to Public Health and Patient Safety

CHANGE
Enhance Complaint Processes and Supporting Systems

FOUNDATION
Change the Mindset and Improve culture

1. Unifying process across Hospira globally
2. Improved process and procedural cohesion
3. Global implementation

World-class leader that anticipates and responds to evolving patient, regulatory and customer needs which contributes to the continuous success of Hospira

1. Implementation of metrics for quantitative feedback
2. Constant management oversight and monitoring of metrics
3. Reactive and proactive response to metrics

1. Unifying process across Hospira globally
2. Improved process and procedural cohesion
3. Global implementation

1. Develop Talent Management for Quality-Minded People
2. Build the Quality Minded Compliance Team
3. Harmonize experience through Communities of Practice

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Quality Lessons

Global process helped in driving consistency across sites

Enhancement of other supporting processes (e.g. Notification to Management, FAR)

Complaint management review served as a common learning platform and launch of global initiatives

Enhancements to the process leads to customer centricity

Positive impact on complaint reduction and cycle time; thereby improving and ensuring patient safety

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Quality Lessons

- Continuously improve investigation quality
- Implement product/process improvements
- Reduce number of registered complaints
- Reduce investigation cycle time
- Reduce product recalls
- Quality becomes competitive advantage

Optimizing Product Lifecycle Never Ends

Assuring Effectiveness of Corrective Actions

- Preventing Repeat Issues
  - Effective CAPA
  - Continual improvement

- Assessing CAPAs
  - Long-term efficacy
  - Monitor post-implementation

Identifying the Right Corrective Actions

- Define
  - Problem Definition
  - Process Mapping

- Measure
  - Gather and Display data
  - Time Series Plot
  - Pareto Chart

- Analyze
  - Process Analysis
  - Brainstorming
  - Analyze Cause & Effect

- Control
  - Standardize and document
  - Control Charts
  - Evaluating results

- Improve
  - Generate and select solutions
  - Pilot and implement solutions

Meera Khullar, Lead Dir., Pharmaceutical Quality Operations – Hospira
PDA / FDA Improving Investigations Workshop, September 18, 2013
Applying Corrective Action Tools

Advanced tools
(Multi-Variant Analysis)

More sophisticated tools
(Process Capability, Green Belt, Black Belt, Human Error)

Basic Six Sigma root cause analysis
(Yellow Belt)

Sharon Timmis, VP Operational Excellence - Pfizer Global Supply
PDA / FDA Improving Investigations Workshop, September 19, 2013

Applying Corrective Action Tools - Example

<table>
<thead>
<tr>
<th>Task</th>
<th>Who does it?</th>
<th>By whom?</th>
<th>Frequency?</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event Control</td>
<td>QA rep</td>
<td>3rd week</td>
<td>Weekly</td>
<td>Use I-MR chart.</td>
</tr>
<tr>
<td>Outliers on Control Chart</td>
<td>Board Facilitator</td>
<td>Investigation to be completed within 1 week</td>
<td>As required</td>
<td>Outliers are Special Causes where the data point is 3 standard deviations away from the average.</td>
</tr>
<tr>
<td>Shifting, Trends and Sawtooth patterns in the Control Charts to be discussed</td>
<td>Board Facilitator and CI team</td>
<td>Investigation to be completed within 1 week</td>
<td>As required</td>
<td>Shifting is 8 points in a row above or below the average. Trend is 6 points in a row increasing or decreasing. Sawtooth is 14 points in a row alternating up and down.</td>
</tr>
<tr>
<td>Set up monthly CI meetings</td>
<td>Board Facilitator</td>
<td>3rd week</td>
<td>Monthly</td>
<td>This is a key element to ensure gains are maintained and that ongoing CI of the system occurs.</td>
</tr>
</tbody>
</table>

Veronica Cruz, PhD - VP, Q&C - Johnson & Johnson
PDA / FDA Improving Investigations Workshop, September 19, 2013

Assuring Effective Corrective Actions

Understanding Root Cause

Establishing Corrective/Preventive Actions

Assuring CAPA Effectiveness

Management responsibility

Example of CAPA Effectiveness

Veronica Cruz, PhD - VP, Q&C - Johnson & Johnson
PDA / FDA Improving Investigations Workshop, September 19, 2013
Corporate Control and Vigilance

Understanding Root Cause
- Investigate to develop knowledge, not to release the batch

Establishing Corrective/Preventive Actions
- Correct the event, avoid reoccurrence, prevent similar events in other areas

Assuring CAPA Effectiveness
- Effective CAPA reduce and control process variation

Management responsibility
- Periodic Quality Systems Review

Verification
- VP, QC
- Johnson & Johnson
- PDA / FDA Improving Investigations Workshop, September 18, 2013

Monitoring CAPA Effectiveness

Workshop Summary

Have the right Team
- Team composition can change when new knowledge is discovered

Be open minded
- Do not go straight to solutions without looking at all relevant data

Senior management and health authority involvement
- Notification processes in terms of timing and level of detail provided
Successfully concluding an investigation is dependent on:

- Effectively getting to the root cause
- Effective CAPAs to prevent repeat deviation
- Effectiveness monitoring ensure the CAPA is correct

Internal company communication with emphasis on:

- Importance of sharing and documenting knowledge gained and lessons learned
- Sharing the information efficiently through the quality system

Participant face-to-face discussions showed:

- Most investigations have similar elements that need to be covered
- There are many ways of conducting a thorough investigation

Each attendee received:

- All case study materials
- Summary of the lessons learned (generated by all the attendees)
- Example of a detailed Points to Consider list for conducting investigations
- A simple root cause analysis tool guide

Acknowledgements

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- Sharon Timmis, Pfizer Global Supply
- Anders Vinther (Genentech/Roche)
- Glenn Wright (Eli Lilly, PDA BOD)