Agenda

• Phase I  Initial Response
• Phase II  Defining an Organized Approach
• Phase III  Comprehending the Gaps
• Phase IV  Remediation & Improvement
• Phase V  Passing the Test!
Defining an Organized Approach

Phase II
Phase II – Defining an Organized Approach

Assignment of Resources

Internal

- Maintaining manufacturing
- In-house process experts

Versus

External

- Completing compliance commitments
- External Quality System experts

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Phase II – Defining an Organized Approach

Quality System Tools for Improvement

- Potential tools for capturing the work include:

<table>
<thead>
<tr>
<th>QS Tool</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPA</td>
<td>Contains all required elements</td>
<td>Visible during inspection</td>
</tr>
<tr>
<td></td>
<td>Structured process</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Documentation retention</td>
<td></td>
</tr>
<tr>
<td>Internal Audits</td>
<td>Some control over visibility</td>
<td>May not contain all required elements</td>
</tr>
<tr>
<td>Quality Plans</td>
<td>Maximum flexibility</td>
<td>Maximum flexibility</td>
</tr>
<tr>
<td>Response Binders</td>
<td>Easy access to information</td>
<td>Too many to list</td>
</tr>
</tbody>
</table>
Phase II – Defining an Organized Approach

Quality system Tools for Improvement

CAPA

Root Cause Investigation
Interim Controls
Solution Development

Corrective and Preventive Actions
Effectiveness Monitoring

Demonstrate Results

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Phase II – Defining an Organized Approach

Quality System Improvement Tool Examples

- Six Sigma DMAIC
- Lean
- Plan-Do-Study-Act
- Supplier Input Process Output Customer
- Root Cause Analysis
- Failure Modes and Effects Analysis
Phase II – Defining an Organized Approach

Management Commitment

- Making Tough Decisions
- Providing Required Resources
- Visible Throughout the Process
- Recognizing the Sacrifice

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Comprehending the Gaps

Phase III
“Finally, you should know that this letter is not intended to be an all-inclusive list of the violations at your firm’s facility. It is your firm’s responsibility to ensure compliance with applicable laws and regulations administered by FDA. The specific violations noted in this letter and in the FDA 483 issued at the close of the inspection may be symptomatic of serious problems at your firm’s manufacturing and quality management systems.”
Phase III – Comprehending the Gaps

Beyond the FDA 483/Warning Letter

• The observations are usually symptoms of a breakdown of an element (or elements) of the quality system.

• It is important to understand the root cause of this failure and to then investigate what other product issues may be impacted by this breakdown.
Phase III – Comprehending the Gaps

Beyond the FDA 483/Warning Letter

• If you get the root cause wrong all corrective and preventive actions will likely be ineffective in resolving the issue.

• Pay attention to the hand-offs between quality system elements.
Phase III – Comprehending the Gaps

Beyond the FDA 483/Warning Letter

• Utilize time tested methodologies for problem solving, such as the DMAIC process:

<table>
<thead>
<tr>
<th>DMAIC Stage</th>
<th>Key Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Define</td>
<td>Make sure the problem statement is written at the system level</td>
</tr>
<tr>
<td>Measure</td>
<td>Collect sufficient data to understand the scope of the issue</td>
</tr>
<tr>
<td>Analyze</td>
<td>Comprehend what is unique, eliminate false assumptions</td>
</tr>
<tr>
<td>Improve</td>
<td>Develop solutions that are Simple, Systematic, and Sustainable</td>
</tr>
<tr>
<td>Control</td>
<td>Conduct thorough, statistically valid effectiveness checks</td>
</tr>
</tbody>
</table>
Phase III – Comprehending the Gaps

Root Cause

Violative Product

Technical Deficiency

Does not meet labeling claims / performance requirements

Process Deficiency

Was not produced per internal and external requirements

Product Deficiency

Quality system Deficiency

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Phase III – Comprehending the Gaps

Risk Management Process

Prioritize Work

Complete Work

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Phase III – Comprehending the Gaps

Documentation

• Provides the proof that you are compliant

• Quality records should stand on their own
Phase III – Comprehending the Gaps

Documentation

Writing a good CAPA file is an art and skill

Be aware of electronic systems limitations

Quality System documentation belongs to the company
Improvement and Remediation

Phase IV
Prioritize
Interim Controls

Investigate

Identify Corrective Actions

Implement

Contain and Control

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Remediation

Time Frame

Document

Rationale
An Example

**Issue**

- Procedures for complaint handling were not adequately established
- Evaluation for the need to perform an investigation was not documented
- No signature of the individual who made the determination
An Example

Action

- Update procedure to require
  - The evaluation is documented,
  - a rationale for why further investigation will not be performed and
  - the signature of the individual who performed the evaluation

- Software update to require this information is populated
An Example

Interim controls

- Documented confirmation that the evaluation was adequately performed and documented
An Example

Remediate

- A look back of complaints with no investigation
- Review to ensure investigations were performed where required
Passing the Test

Phase V
Manage Communications

Communicate
- Request a meeting
- Prepare
- Communicate plans

Demonstrate
- Follow through
- Provide documents

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Manage Communications

- Determine Frequency
- Written and Face to Face
- Milestones
Re-Inspection Process

System

Support Process

Subject Matter Experts

Prepare

Practice

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Know Your Vulnerabilities

System

Subject Matter Experts

Support Process
**Definition**

- A simulated inspection is a practice session designed to prepare subject matter experts to represent both general and specific topics during an inspection.

**Who**

- Conducted by independent personnel

**Methods**

- Likely and/or difficult inspection questions are asked and the SME answers as they would during an inspection
- Experiential learning
Simulated Inspection: Outcomes

- SME performance
- Topic Risk

Feedback

Follow Up

- SME
- System
- Support

- Results
- Management team

Review
Questions