

Auditing a Deviation Management System

Title: Auditing a Deviation Management System					
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Audit Training Manual: 04

**Auditing a Deviation
Management System**

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incident had not been correctly identified and/or that the actions determined had either not been taken in a timely manner, or had not effectively addressed the root cause.

Reportable Result(s): The final value(s) that will be reported as representing the outcome of the analysis derived from the data. It is the value compared to the specifications.

Resample: To take additional test samples from the same lot of material previously tested.

Retest: To perform additional testing on the original sample (where possible) or new original sample according to an investigative plan, when no determinant error is found.

Root Cause: The basic cause of a deviation, from which effective actions can be defined to prevent recurrence.

Trend: A determination that data is moving in a general direction based on the reoccurrence of events within a defined period of time.

Undetermined laboratory error: A situation where the laboratory investigation is inconclusive and the possibility remains that a laboratory error has eluded the investigation process.

Explanation of Topic

Introduction

During manufacturing, unplanned events or incidents may occur. These events are considered deviations from established processes, procedures and policies possibly placing the product out of compliance with regulatory requirements and jeopardizing the safety, purity and effectiveness of the drug product.

Deviations may be referred to by many different names such as atypical events, discrepancies, problems, abnormal occurrences, events or incidents.

There must be a deviation management system in place to determine the extent of the deviation, the impact of the deviation and to investigate why the deviation occurred and what can prevent it from reoccurring.

The goal of this training module is to describe how to audit a deviation management system using the appropriate GMP standards. The GMP requirements detailed in this module should be applied to the supplier on a sliding scale, the scale being dependent on the product or service being audited. In addition, the auditor should consider the risks associated with an unplanned incident that would potentially result in product not meeting customer specifications or regulatory requirements.

The principles outlined in this module can apply to a quality management system based on ISO 9001 or other similar systems as well as GMP. An example of a supplier where this might be the case is a supplier of a Non-contributory raw material.

It is, however recognized that there are differences in nomenclature and the requirements between ISO 9001 and GMP. For example, a deviation in a quality system based on ISO is often identified or defined as a 'non-conformance'. A 'non-conformance' or 'non-conforming product' can be:

- Product not meeting specification.

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- Ø Requirements for management review
- Ø How an investigation to determine root cause should be performed
- Ø What data should be examined during the investigation
- Ø What the immediate corrective actions are
- Ø What the retention time is for keeping investigation reports
- Ø Who should approve the final report
- Ø What material and/or lots should be considered /impact on associated batches
- Ø Roles and responsibilities for various departments
- Ø Who should follow up on implementation of corrective or preventive actions

The deviation management system should encompass the manufacturing, testing, control, and distribution of finished drug products and materials.

The SOP should also include information about trending deviations. Deviations should be analyzed for trends. If a shift or trend is detected, it should be communicated to management and the department where the deviation has taken place.

Roles and Responsibilities for Investigating a Deviation

Many departments or functions may be involved in the process of investigating a deviation. Each may play a different part. Specific roles are outlined below.

Originator of the deviation

The department or function where the deviation was found/discovered is usually considered the "owner" of the deviation. As such, the owner has the responsibility to investigate the cause of the deviation, analyze data surrounding the investigation, and determine what actions can be taken to correct and/or prevent the deviation from reoccurring. The originator is also responsible, according to site procedure, for writing up the investigation report.

Quality Assurance (QA)

Because QA is responsible for determining the disposition of a product, it needs to be involved in the investigation process. QA should be notified immediately when a deviation is detected. Management and Quality Assurance are responsible for approving conclusions and actions taken or identified as a result of an investigation. It is also the responsibility of Management and/or Quality Assurance to ensure that appropriate communication with other impacted functions/sites has taken place as well as to provide copies of final (and interim) reports as appropriate. QA is also expected to oversee the investigation and ensure that it is adequate. The department responsible for the deviation is expected to conduct the investigation. QA should review and approve all deviation investigations associated with all batches of manufactured product prior to releasing product batches.

Other functions or departments

Depending on the extent of the deviation, it may impact other batches of product or other products. Other departments may provide data and information to be used in the investigation. An example might be a pump breaking in an aseptic area. Environmental monitoring data may be examined to ensure that the filling environment was within specification during the incident. In the case of an OOS, product lots that are not directly impacted by OOS results but are linked to the root cause should be identified and evaluated.

Additional departments that may be included in the investigation are Purchasing, Technical Operations, Stability, Regulatory Affairs and/or other departments depending on the type of investigation.

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of the deviation.

- Evaluation of Quality impact considers
 - o Product safety and integrity
 - o Product purity and efficacy
 - o Product stability
 - o Customer perception and potential complaints
- Evaluation of Regulatory impact considers
 - o Any deviations from regulatory commitments and any resulting regulatory reporting requirements
- Evaluation of Compliance impact considers
 - o GMP violations or deviations from regulatory guidance
 - o Revalidation/re-qualification requirements

g. Corrective and Preventive Actions

Corrective actions are developed to support the affected batch(es) by correcting or eliminating the causes of the deviation. Preventive actions are developed to avoid recurrence. Both corrective and preventive actions are listed with targeted timeframes for implementation, are assigned a responsible person, and must be monitored to completion.

h. Documentation and Approval

Reports should be well-organized and easily understandable by a third party. Supporting documents should be attached, unless referenced as controlled documents. Casual e-mails should be avoided.

- Investigation reports should include basic information:
 - o Unique identification number
 - o Date deviation reported
 - o Product, potency, lot number
 - o Processing step or phase of operation
 - o Important dates such as manufacturing, packaging, labeling & testing
 - o Identification of materials used in the batch and equipment/instruments used for manufacture/testing

Investigation reports and associated data is reviewed and approved by Quality and Management and are typically completed within 30 working days. If additional data is required to determine the disposition of the lot and the investigation cannot be completed within 30 working days, provisions should be in place to document and approve any necessary extensions.

Reports must be approved prior to QA release of material.

i. Tracking Corrective and Preventive Actions

A system should be in place to track implementation of corrective and preventive actions. Typically, corrective actions are completed prior to the lot release while preventive actions are implemented after release. Any extension of the agreed implementation date should be approved.

j. Trending root causes

A system should be in place to detect any trends associated with deviations and root causes. A procedure should clearly define what the site considers a trend and the steps to follow if a trend is detected. Trends may be identified according to product, root cause and/or GMP systems.

Each site should have an understanding of its key deviation issues. Operations sites might use Process Behavior Charts (PBCs) to trend key parameters.

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Documentation includes initialing and dating by involved person. If a laboratory result is to be invalidated, the laboratory should provide documented proof and justification for invalidating the result. In addition, the investigation should extend to other samples that may have been tested by the same analyst or using the same equipment.

If the original sample is judged to have been prepared improperly or not representative of the batch, the batch may be re-sampled using the same procedure and method as the original sample according to a pre-approved testing and sampling plan. If the original sample was not sampled correctly or the sampling method was in error, a new accurate method should be developed, qualified and documented. Other batches using the previous faulty sampling method will be assessed.

If the initial laboratory investigation is inconclusive, the possibility exists of an undetermined lab error and a pre-approved extensive retesting program may be initiated.

Once the lab error is eliminated as the cause and the Out of Specification result has been confirmed, the investigation now becomes a full or manufacturing investigation. It then follows the investigation procedure indicated in the “**Investigation Components**” section of this document.

In the case of an inconclusive manufacturing investigation, the possibility still remains that a laboratory error eluded the OOS investigation process. The investigation may return to the laboratory to further investigate the possibility of an undetermined lab error. OOS investigations should be periodically evaluated for trends.

Some of the principles described here are applicable to observed OOT results. OOT results should be documented and there should be an initial laboratory assessment to see if there is evidence of a laboratory error. Retesting may be appropriate if a confirmed laboratory error is found, otherwise the result is accepted. The assessment and implications should be documented.

Summary

Incidents during manufacturing and testing may occur that can affect the quality attributes of a drug product. These deviations must be acknowledged, analyzed and investigated to determine the root cause. There should be a defined system in place to manage deviations.

Investigations should explore all possibilities and eliminate those that are not supported by data. Investigations should follow a prescribed format and determine root cause. Once the root cause has been determined and a conclusion drawn, the company should implement corrective and preventive actions to prevent the same incidents from happening again. These corrective actions/preventive actions should be tracked with implementation status being communicated to management.

Key Parameters for Auditing a Deviation Management System

Prior to the audit

- Determine what manufacturing processes are used at the site.
- If available, review the list of deviations generated at the site or company.
- Review complaints to ensure that corresponding investigations are in place, as applicable.