Goals

When you have completed this module, you should be able to:

- Perform an audit of a deviation management system
- Use a range of tools and information, including the contents of this unit to support the audit of a deviation management system
- Understand and apply appropriate GMP standards/regulations and In-house standards to an audit of a deviation management system
- Recognize compliance or non-compliance of deviation management systems to applicable regulations

Definitions

Corrective Action **:** An action taken to correct or eliminate the causes of an existing deviation, issue, incident or problem. A corrective action must typically be completed before the disposition of any implicated materials can be determined.

Deviation: Departure from a process/procedure or an unexpected result.

Investigation: A formal and documented review of a deviation, issue, incident or problem, to identify its root cause and determine the actions required to address it.

Laboratory Error **:** Incorrect performance of one or more of the steps of an analytical procedure and/or any identifiable laboratory related problem such as malfunctioning equipment, etc.

Out of Specification Test Result (OOS): A laboratory test result that is outside its regulatory or compendial limits. In some cases, there may be additional tests and/or limits that are used to assess the quality of a material, but are not included in registrations or compendia. In these cases, the general principles described here are useful, but more latitude is allowable in the disposition of the material as long as it meets its legal requirements.

Out of Trend Test Result (OOT): A laboratory test that is within its regulatory or compendial limit but is atypical of previous results for the test over a number of batches or earlier time points in a stability study and may provide early indication of a potential OOS result.

Overdue Investigation: If after 30 working days of the incident, neither an interim nor final investigation report has been **approved**, the investigation is overdue.

Preventative Action/Measure**:** An action taken to prevent recurrence or to pre-empt a potential issue, deviation, incident or problem.

Process Capability: A statistical indicator that measures how well a given process is running. It compares the actual variability in the process to the process specification.

Reanalysis (New Initial Test): A test performed on the original sample (where possible) following invalidation of a test for a determinant error.

Repeat deviation: A deviation that re-occurs after the identification of actions identified

Deviation

- 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.

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

Recurring problems may indicate that the root cause(s) were not completely identified and/or that preventive actions were not effective. A system should be in place to report significant or recurring problems to management.

Regulatory Expectations for Laboratory Testing

Since laboratory test results are used to release product, any out of specification (OOS) result must be thoroughly examined and investigated. FDA expectations, based on the Barr laboratories legal decision in 1992, are that:

- A test result not meeting specification will be highlighted and investigated (usually within 30 working days)
- The word "failure" means any out of specification (OOS) result
- Product can not be "tested" into compliance
- Companies cannot average passing and failing test results to obtain a passing result
- Retesting is not the first action to occur after an OOS is generated
- Failing test results are not automatically discarded because they are assumed to be laboratory error
- Initial test results cannot be discounted after retesting different parts of the batch
- Companies can not discard initial failing results when passing retest results are achieved

Out of specification (OOS) and Out of trend (OOT) test result

Out of specification test results can be obtained when materials and finished product are tested. They can also be obtained during stability testing. The testing can be chemical, physical or microbiological.

When the analyst reports an initial OOS, the laboratory supervisor or designee will conduct a limited investigation. The supervisor or designee will try to determine if the result could be a result of an instrument malfunction, an error by the analyst or a lab error. This investigation must be documented. The original samples and test solutions should be kept until all testing is completed and approved to confirm or eliminate these possible causes of errors.

To eliminate probable causes the supervisor or designee should:

- Verify analyst's knowledge of and performance of correct procedure including rechecking all calculations
- Examine raw data and identify anomalous or suspect information
- Confirm performance and calibration of instruments and system suitability requirements
- Verify that appropriate reference standards, solvents, reagents and other solutions were used and met QC specs and expiration dates
- Verify that the test method was performing to standard

Once all of the data is gathered from this limited or preliminary investigation, all findings are documented, preserving all evidence.

If lab error is determined as the cause, depending on the error, the laboratory should follow an approved procedure describing under what conditions must be met for a lot