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Laboratory Investigations- A Regulatory Perspective

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Code of GMP Requirements

- Any significant deviations are fully recorded and investigated [1.3vi]

- Any deviations are fully recorded [1.4iv]

Definition

- What are OOS, OOT or Atypical results?
  - OOS includes all test results that fall outside specifications or acceptance criteria established by the manufacturer and /or laboratory
  - OOT are results which fall out of trends. These may or may not be OOS
  - Atypical results are usually anomalies or unexpected results from testing of similar starting materials or products. These may or may not be OOS

Investigation

- Why do we need to investigate?
  - to determine the cause of the OOS
    - laboratory based error
    - Manufacturing failure
- If a batch is rejected do we still need to do investigation?
  - yes! to see if other batches or products are affected
  - identification and implementation of corrective and preventative action

Investigation

- The investigation must be :
  - Thorough
  - Timely
  - Unbiased
  - Scientifically sound
  - Well documented

OOS investigation

- Investigation into possible laboratory based failure

  -assessment of accuracy of the laboratory data to determine if it is

  - analyst error
  - equipment related
  - procedural

  Ideally this should be done before test samples and reagents are discarded to determine validity of the original data

OOS investigation

- If the investigation shows no assignable cause, for the laboratory based failure i.e. OOS is confirmed, then full scale manufacturing investigation should be conducted

- Objective
  - to identify scope and root cause
  - Identify and implement corrective and preventative action

Laboratory investigation

- Matters that should be investigated for assignable cause :
  - inadequate training of analysts
  - poorly maintained or improperly calibrated equipment
  - analysts not following procedures
  - procedures technically not appropriate
  - validated procedures
  - reagents
  - consumables
  - cleanliness of glassware
  - etc

Laboratory investigation

Outcome is to :

- confirm if OOS is true OOS
- determine source of OOS and
- take corrective and preventative action as appropriate

Laboratory investigation

Adequate documentation of the investigation must be kept :

- monitor trends
- management should be alerted to developing trends
- ensure problem areas are addressed

- Do I re-test or re-sample?

Re-testing

- When to re-test?
  - for a laboratory based failure whenever possible test the original sample
  - if there is no laboratory based failure then there is no reason to re-test

Re-testing

- Re-testing criteria involves testing the original sample
- Re-test may be due to:
  - possible sample preparation problem eg dilution error
  - instrument malfunction
- Consider another analyst for re-test
- Need to define number of re-tests in procedure
  - don't "test into compliance"

Re- sampling

- Conditions for re–sampling :
  - when original sample was taken not following procedure
  - when there was doubt with sampling procedure
  - ensure sample is representative of the batch

Re- sampling

- Re-sampling involves:
  - another sample not being the original sample

- Re-testing of the original sample
  - should be performed by the same test method that was used to test the original sample

Reporting results

- Averaging
  - Appropriate versus inappropriate uses?

- Appropriate uses
  - for example in cases where the average is reported as the test result eg optical rotation
  - if sample is homogenous
  - microbiological assays due to innate variability in the biological test system

Reporting results

- Inappropriate uses
  - Averaging of results where individual results should be provided eg uniformity determination
  - Additional testing as a result of OOS where all the results are averaged i.e. OOS results and the additional retest or resample results

OOS test results should not be averaged

All individual results should be presented to the quality unit for approving or rejecting of the drug product or in process material

Reporting results

- Outlier results
  - the possible use of outliers should be defined, be statistically valid and documented
  - outlier results are not applicable in cases where the variability in the product is what is being assessed, such as content uniformity and dissolution. In these applications a value seen as an outlier may in fact reflect a non-uniform product
  - The OOS should not be discounted unless it can be discounted

Concluding the investigation

- If the OOS is confirmed the result should be used in evaluating the quality of the batch or lot

- For inconclusive investigations when there is no cause for OOS and the OOS result is not confirmed the OOS should be given consideration in determining the batch or lot disposition

Contract laboratories

- If the contract laboratory has product specifications then the laboratory is obliged to conduct OOS investigation

- If the contract laboratory doesn't have product specifications then the test results should be provided to the manufacturer who will report the OOS investigation
  - the contract laboratory OOS would be limited to review of things such as the equipment calibration, instrument, reagents and reference standards, analyst training etc

Contract Laboratories

- A focus of the TGA is that information flows from the laboratory to the manufacturer including handling of all OOS

- The arrangements need to be agreed and documented in the GMP agreement

Examples of deficiencies

- No OOS system available, however, examples were observed at the audit
- Automatic retest without justification
- Poor investigation
- Recurring problems and no root cause determined
- Making a recommendation from OOS and not following through with CAPA system

GMP audit

- At GMP audits some items we would expect to see include the following:
  - There is an OOS system
  - With OOS there is full investigation and a CAPA system
  - Good documentation
  - OOS results and investigations need to be reviewed at regular intervals
    - is the issue isolated or widespread?
    - are there trends?

GMP audit

- All OOS results should be documented
  - we would be more surprised if no OOS were available
- All manufacturers and contract laboratories should have an OOS system
- OOS entries should be investigated and closed in a timely manner

The list is huge!!!!

Thank you for listening