Laboratory Investigations- A Regulatory Perspective

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Contents

• Code of GMP requirements
• Definition
• Investigation
• Laboratory errors
• Re-testing versus Re-sampling
• Reporting results
• Concluding the investigation
• Contract laboratories
• Examples of deficiencies
• GMP audit-expectations
• Any significant deviations are fully recorded and investigated [1.3vi]

• Any deviations are fully recorded [1.4iv]
• 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
• 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
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
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?
• 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 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
• 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
• 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
• 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
• 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
• 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