Guideline/SOP: Handling of Laboratory Gross Errors/Data History

Introduction

Laboratory gross errors are events in the laboratory that may produce erroneous results and can be usually attributed to either analyst related errors or instrument related errors. These types of errors should be accounted for by performing an abbreviated investigation as well as retaining this data. This procedure will outline a simple yet effective way that manufacturers can manage these types of laboratory events in an efficient manner which will also ensure data integrity is maintained.

This guideline covers a process to maintain data integrity as related to handling laboratory "Gross Errors". Gross errors in the laboratory can occur with or without the generation of data. This procedure covers cases where gross errors have occurred in the laboratory and data has been generated that is associated with these gross errors.

A laboratory "Gross Error" is an event in the laboratory that occurs for two primary reasons; either due to analyst error or instrument error. These types of errors can occur with or without the generation of data. When data is generated, the data is inherently erroneous since it has been generated in the presence of a gross error. These types of erroneous results due to these types of events are usually immediately obvious to the laboratory analyst. Below is a partial list of these types of analyst and instrument "Gross Errors".

1. Incorrect Sample
2. Incorrect Standard Preparation
3. Incorrect Sample Weighing
4. Wrong Diluent Used
5. Wrong Diluent Volume
6. Mobile Phase Preparation Error
7. Improper Mixing of Mobile Phase
8. Incorrect pH Adjustment
9. Incorrect HPLC/GC Set up and Run
10. Wrong Injection Volume
11. Wrong Detector Wavelength
12. Incorrect Injection Sequence
13. Uncalibrated Instrument Used
14. HPLC/GC Auto Injector Malfunction
15. Lamp Intensity Failure
16. Column Leak, Poor Plate Count, Poor Resolution
17. Power Failure
18. Plumbing Problem/Leak

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Purpose

To establish a general procedure within the QC laboratory to properly manage laboratory "Gross Errors" in order to meet applicable GLP and GMP standards ensuring data integrity is maintained and ultimately product quality.

The purpose of the investigation of OOS/atypical results is to determine whether the cause of the atypical result is due to a manufacturing error or a laboratory measurement error, and to identify the root cause. The purpose of this guideline is to describe the procedure to identify and handle obvious laboratory errors, or gross errors.

Responsibility

Analysts are responsible for recognizing the need for an investigation, initiating a laboratory investigation, immediately reporting any OOS or atypical results to a supervisor, and for preserving and properly storing all solutions and standards used in the test measurement.

Supervisors or laboratory heads are responsible for the overall conduct of the laboratory investigation.

Quality Assurance is responsible to monitor investigations and track atypical results to ensure that corrective and preventative actions are adequate to prevent repetition of the error that caused the atypical result, whether due to manufacturing or measurement errors.

Scope

This procedure applies to all rest results that fall outside of established specification (OOS), are out of trend (OOT) compared with previous results (for example, in the case of stability data, trend analysis of manufacturing parameters, etc.), or are in any other way atypical of expected results. The procedure also applies in the case where procedural errors or equipment errors or malfunctions are detected, whether or not the test is complete, regardless of whether or not data have been obtained.

This procedure applies to physical, chemical, and microbiological tests used for release and stability testing on pharmaceutical products and other GMP batches, and their associated manufacturing components (raw materials, excipients, and packaging components).

This procedure is not applicable to research/development testing, or for method development and validation. Any investigation required during method validation follows the appropriate SOP for method validation.

Procedure

1. When an analyst obtains atypical results, or when the analyst becomes aware of laboratory or procedural errors that were committed during testing, he or she will: 1) annotate the atypical results or known laboratory error in the appropriate lab notebook, 2) notify the lab supervisor immediately, 3) initiate filling out the Laboratory Investigation Report (this blank report will be an attachment to the guideline used in each factory), and 4) properly preserve all starting materials, solvents, intermediate and final solutions, and standards used in the testing. These materials will be retained and preserved until completion of the investigation or until it has been determined that they are no longer useful.

2. Laboratory investigations will be initiated within one (1) business day of the discovery of the OOS/atypical result, and will be completed within ten (10) business days, unless an extension is approved in writing by the laboratory supervisor and QA.

3. The supervisor will immediately review the results, the lab notebook, the starting materials and all solutions, the raw data, and the calculations used to generate the final results. A laboratory investigation gross errors review will be completed using the Gross Errors Checklist (a blank Gross Errors Checklist will be an attachment to the guideline used in each factory). The checklist will be completed by the supervisor and analyst together. The supervisor will interview the analyst, and will check relevant documents, in order to answer questions which will help identify whether common or obvious laboratory errors (gross errors) were the root cause of the OOS/atypical result. These questions will include the following, provided as examples, and not intended to be inclusive:

   - ✓ Was the analyst trained on the test method?
   - ✓ Was the latest version of the method being used?
   - ✓ Was the proper test method being used?
   - ✓ Was the test method procedure followed properly?
   - ✓ Does the notebook documentation indicate any procedural errors were made?
   - ✓ Does the review of the starting materials, solvents, solutions, glassware, and laboratory work area indicate that any obvious errors were committed?
   - ✓ Was the correct sample used?
   - ✓ Was the sample spilled or contaminated before testing?
   - ✓ Was the proper reference standard used, and was it prepared properly?
   - ✓ Are the laboratory environmental conditions within the proper ranges (for example, temperature and humidity)?

- ✓ Was the instrument used within the calibration period?
- ✓ Was the instrument set up properly, and does it appear to be functioning properly?
- ✓ Are there any instrument error codes indicating problems with the instrument?
- ✓ Did the system suitability tests meet all requirements?

- ✓ Do the raw data, including chromatograms, spectra, etc., reveal any suspect information (for example, improper integration, etc.)
- ✓ Was there a power failure during the measurement time?
- ✓ Was there any other interruption of the measurement process during the measurement time?
- ✓ How do the results compare with test results from the method validation?
- ✓ How do the results compare with other tests performed on the same lot of material?
- ✓ How do the results compare with historical results from the same material?

4. The supervisor will indicate on the Laboratory Investigation Report form whether the review has uncovered a clear laboratory error (gross error) as the cause of the OOS/atypical result, and will identify the specific source of the laboratory error. If this is the case, then an assignable cause has been found, and the original result is voided and the analyst repeats the test. The investigation findings are documented on the Laboratory Investigation Report and the investigation is closed.

5. If other samples were tested at the same time as those for which the assignable cause was found, these will be evaluated for impact from assignable cause by the supervisor and this will be recorded in the investigation report.

6. If no assignable cause is found, a full investigation will be completed involving both manufacturing as well as the QC laboratory, since the origin of the OOS/atypical result is unknown. These will be handled as full investigations outside of the gross error process since those types of either OOS, OOT, or deviation results may be attributed to product quality. A full investigation is needed to determine if the result is valid or not.

7. If a laboratory error is suspected to have been committed, then the supervisor will create an experimental plan to determine whether the suspected laboratory error was the cause of the OOS/atypical result. The reasons and scientific rationale for re-measurements and/or re-dilution will be documented in the investigation report.

8. In some cases, the original test solution may be re-measured following the method to confirm the OOS/atypical result.

    a. If the re-measured results do not confirm the original result, instrument inconsistency may be suspected to be the assignable cause. If this is verified through re-measurements, then the original OOS result is voided, the re-measured results are reported, and the investigation is closed.
    b. If original diluted solutions for measurement are not available, re-dilutions may be made.
    c. If any of the re-measurements confirm the original OOS result, a full investigation is needed.

9. If the original test solution is suspected, re-dilution of the stock or intermediate sample preparations can be measured.

    a. If all re-measured re-diluted results do not confirm the original OOS result, and meets acceptance criteria, then dilution error may be the assignable cause. If this is found to be the case, then the re-dilution results from the re-measurements are accepted. The original OOS result is voided and the investigation is closed.
    b. If the re-dilution results do not confirm the OOS results, other factors such as insufficient mixing, sonication, shaking, etc., may be suspected as the assignable cause. The results are recorded in the investigation. The original OOS result is voided. Re-test the sample according to the method and with correction of the assignable cause.
    c. If any of the re-dilution results confirm the original OOS result, a full investigation is needed.

10. The Investigation Plan and justification must be documented and signed by the supervisor in the investigation report.

11. If new results from the investigation are within acceptance criteria, and assignable cause is determined, the new results are accepted and reported, and the Laboratory Investigation is concluded.

12. If the new results from the investigation confirms the OOS/atypical result, a full investigation is needed.

13. The data that may be generated in the presence of a gross error should be maintained. This data is not part of the final data set (Data history) and reported results related to the product's quality, since it was generated in the presence of an obvious error that caused the erroneous results, and therefore the results are invalid. However, the investigation will be documented with the final data set.

14. This type of laboratory investigation should be abbreviated and consists of the following at a minimum, which is to be recorded in the laboratory investigation report:

    a. Analysis date, sample ID, instrument, analyst, and other pertinent information
    b. Documented SOP/Test method followed
    c. Description of the error
    d. Reason for the error and justification
    e. Corrective and Preventative action
    f. Location of data archival

15. When an assignable cause is found for a laboratory error (gross error), an appropriate corrective and preventative action plan (CAPA) must be written and implemented. These CAPA actions will be recorded in the laboratory investigation report, conclusions section.

16. When an assignable cause is found for a laboratory error (gross error), all other testing of all materials which may have been affected by the same assignable cause will be evaluated for possible impact. This evaluation will be recorded in the laboratory investigation report, conclusions section.

17. The investigation of the data generated as a result of a gross error should be maintained for the same period of time as the rest of the laboratory data (Data History).

Example

For example, when running a duplicate HPLC analytical assay, if one of the chromatograms is out of specification (or the data is determined to be erroneous) and the other chromatogram is in specification, then the supervisor will undertake an investigation. If the supervisor determines that the cause of the poor result is due to a gross error, a gross error investigation report should be completed and the data related to this gross error disregarded, but still retained and documented along with the investigation.

The supervisor will then propose a written corrective action. This corrective action should consist of steps to be taken on: 1) how to treat the erroneous data, 2) how to move forward with the current analysis and valid data, and 3) how to prevent the gross error from occurring in the future. To move forward with the analysis, in most cases would involve weighing and running new samples (in the case of sample preparation gross errors) or re-inject already prepared samples in the case of instrument failures, and non-sample preparation related gross errors. If these new sample preparations/reinjections comply, then the new sample results will be treated according to the OOS/OOT procedure, along with the original passing sample result, and the final result recorded. The one erroneous chromatogram due to a gross error identified in the investigation (mentioned above) should be saved, and not deleted, and the chromatogram, along with the investigation and all other corresponding results, fully documented so that the erroneous result can be fully explained upon review.

Flow Charts

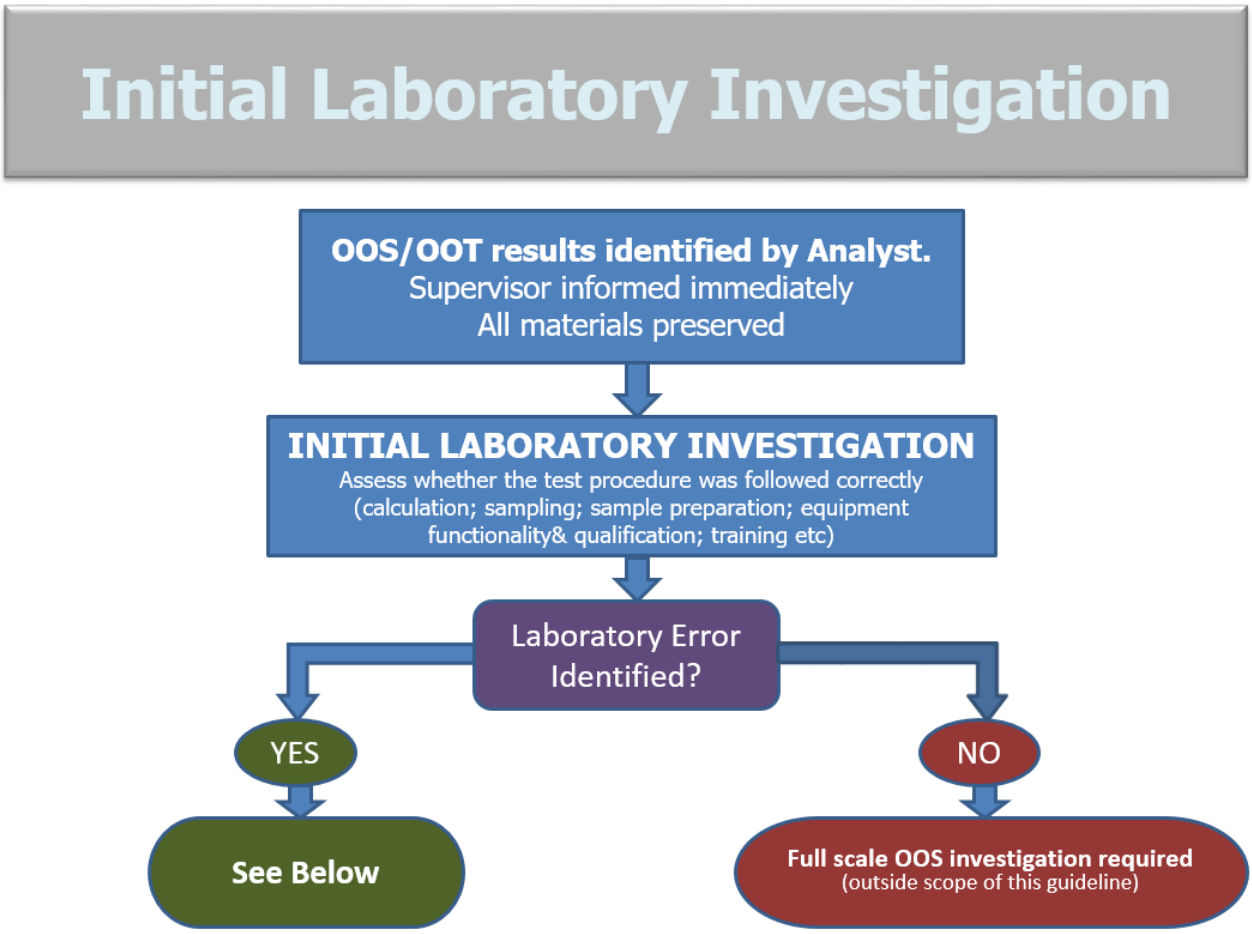

Figure 1 – Need for Laboratory Investigation arises due to OOS/atypical results or known laboratory error.

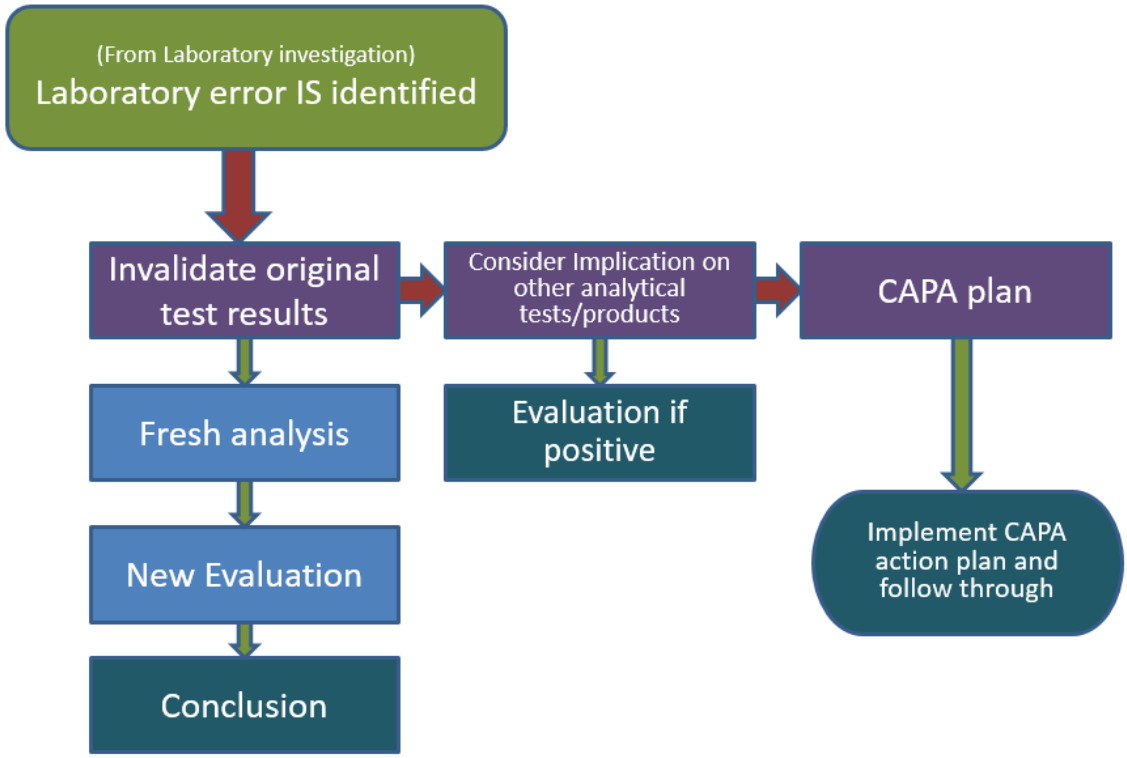

Figure 2 – Procedure resulting from assignable cause found during laboratory investigation.

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