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Evaluation and Reporting of Results Annex 1B

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ANNEX I B OF THE OMCL NETWORK GUIDELINE

“EVALUATION AND REPORTING OF RESULTS”

RESPONSIBILITIES OF THE LABORATORY SUPERVISOR

Extract from the FDA Guidance for Industry “Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production”, chapter III B: Responsibilities of the Laboratory Supervisor

Once an OOS result has been identified, the supervisor's assessment should be objective and timely. There should be no preconceived assumptions as to the cause of the OOS results. Data should be assessed promptly to ascertain if the results may be attributed to laboratory error, or whether the results could indicate problems in the manufacturing process. An immediate assessment could include re-examination of the actual solutions, test units, and glassware used in the original measurements and preparations, which might provide more credibility for laboratory error hypotheses.

The following steps should be taken as part of the supervisor's assessment:

1. Discuss the test method with the analyst; confirm analyst knowledge of and performance of the correct procedure.
2. Examine the raw data obtained in the analysis, including chromatograms and spectra, and identify anomalous or suspect information.
3. Verify that the calculations used to convert raw data values into a final result are scientifically sound, appropriate, and correct; also determine if unauthorized or unvalidated changes have been made to automated calculation methods.
4. Confirm the performance of the instruments.
5. Determine that appropriate reference standards, solvents, reagents, and other solutions were used and that they meet quality control specifications.
6. Evaluate the performance of the testing method to ensure that it is performing according to the standard expected based on method validation data and historical data.
7. Fully document and preserve records of this laboratory assessment.

The assignment of a cause for OOS results will be greatly facilitated if the retained sample preparations are examined promptly. Hypotheses regarding what might have happened (e.g. dilution error, instrument malfunction) should be tested. Examination of the retained solutions should be performed as part of the laboratory investigation.

Examples:

- Solutions can be re-injected as part of an investigation where a transient equipment malfunction is suspected. Such hypotheses are difficult to prove. However, reinjections can provide strong evidence that the problem should be attributed to the instrument, rather than the sample or its preparation.
- For release rate testing of certain specialized dosage form drugs that are not destroyed during testing, where possible, examination of the original dosage unit tested might determine whether it was damaged during laboratory handling in a way that affected its performance. Such damage would provide evidence to invalidate the OOS test result, and a retest would be indicated.
- Further extraction of a dosage unit, where possible, can be performed to determine whether it was fully extracted during the original analysis. Incomplete extraction could invalidate the test results and should lead to questions regarding validation of the test method.

It is important that each step in the investigation be fully documented. Laboratory management should ascertain not only the reliability of the individual value obtained, but also the significance these OOS results represent to the laboratory quality assurance program. Laboratory management should be especially alert to developing trends. As part of an effective quality system, a firm's upper management should appropriately monitor these trends and ensure that any problematic areas are addressed.

Laboratory error should be relatively rare. Frequent errors suggest a problem that might be due to inadequate training of analysts, poorly maintained or improperly calibrated equipment, or careless work. Whenever laboratory error is identified, the firm should determine the source of that error and take corrective action to prevent recurrence. To ensure full compliance with the CGMP regulations, the manufacturer also should maintain adequate documentation of the corrective action.

In summary, when clear evidence of laboratory error exists, laboratory testing results should be invalidated. When evidence of laboratory error remains unclear, a full-scale OOS investigation should be conducted by the manufacturing firm to determine what caused the unexpected results. It should not be assumed that OOS test results are attributable to analytical error without performing and documenting an investigation. Both the initial laboratory assessment and the following OOS investigation should be documented fully.