

# How to Investigate Out-of-Specification Results

By Jerry J. Kolaitis and Susan M. Mondabaugh, PhD

Companies can spend considerable time and resources investigating out-of-specification (OOS) results obtained at various stages of in-process testing, release testing and/or stability testing of products (including both drug substances and dosage forms). The goal of any OOS investigation is to identify the root cause of the OOS result and provide the scientific justification for any corrective action. Conducting timely, thorough and well-documented OOS investigations is critical both to ensuring product quality and integrity and to avoiding inspectional observations by regulatory authorities. The key elements to conducting successful OOS investigations are reviewed in this article.

## Background

Manufacturing of drug substances, drug products and excipients is conducted in accordance with current Good Manufacturing Practice (cGMP). The elements of GMP are delineated in regulations, and national and international guidance documents. In the US, the Food and Drug Administration (FDA) has codified GMP in 21 CFR Part 211. The regulations and guidance documents pertinent to OOS investigations are listed in **Table 1**.

GMP regulations require the investigation of problems that could affect the safety and efficacy of drug products. Examples include rejections, deviations, complaints, recalls, stability failures, yield discrepancies, packaging/labeling inconsistencies, cross-contamination, nonsterility of injectable products and general failure

to meet specifications. The regulations also require that an investigation be performed whenever an OOS test result is obtained in order to determine the cause. Any investigation, including

Both the departments of quality assurance (QA)/quality control (QC) and regulatory affairs need to be involved in the process. The QA department must be involved in every phase of the investigation and, in certain cases, it should be the investigative unit. The extent that regulatory affairs needs to be involved depends upon the nature of the problem and the corrective action that needs to be taken. At a minimum, regulatory affairs should be notified.

In order for an OOS investigation to be successful, a procedure must be available and all pertinent personnel must be trained in it. The procedure must address each of the following:

- Personnel qualifications and training
- Timeframes for completing actions
- Precise retesting and resampling criteria
- Number of retests allowed
- Necessity of reaching a scientifically sound conclusion
- Review and approval requirements
- Necessary documentation
- Cross-functional assessment of potential issues related to safety and/or lack of efficacy if product has been commercially distributed
- Regulatory authority notification requirements (e.g., if the final result indicates that a marketed lot no longer meets its established specifications, FDA must be notified via an NDA-Field Alert Report).



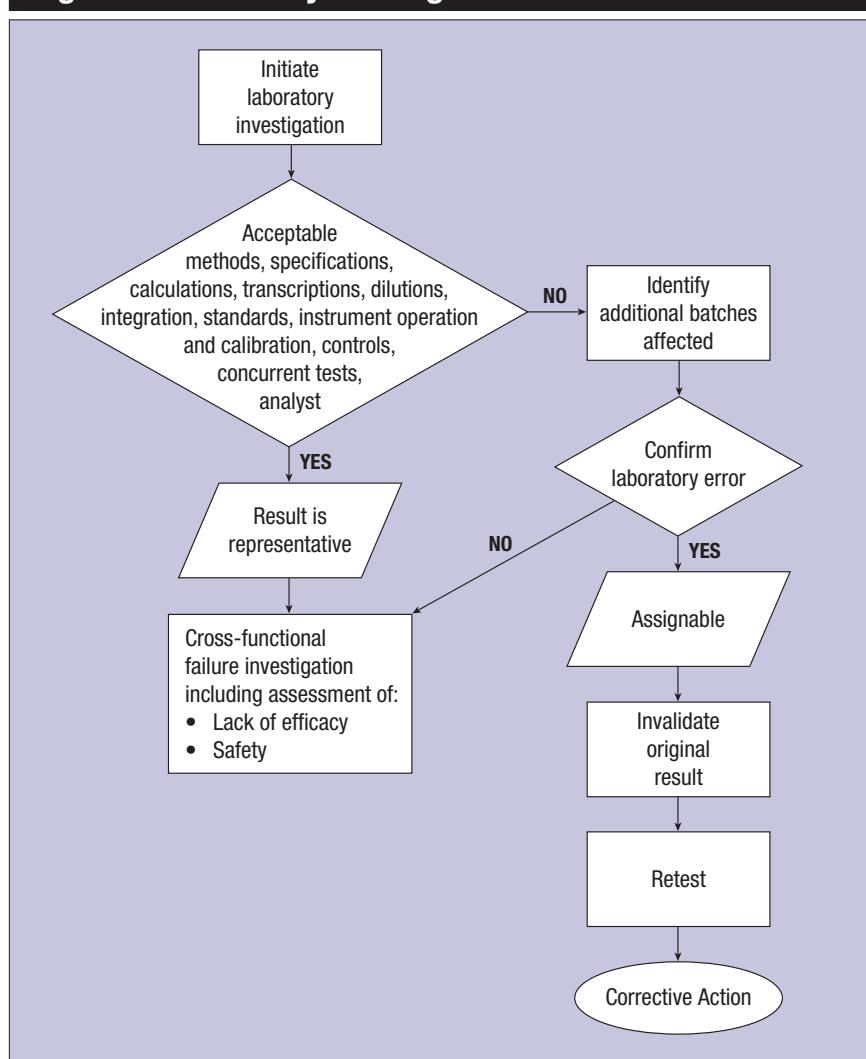
that of an OOS result, needs to be conducted and documented according to a standard written procedure.

## Key Elements

The key elements for conducting successful investigations are identifying the problem, preparing an investigational plan, executing the plan and assessing the investigation's outcome.

**Table 1: Regulations and Guidance Documents**

Regulations and Guidance Document	Title
21 CFR Part 211	Current Good Manufacturing Practice for Finished Pharmaceuticals
ICH Q7A (August 2001)	Good Manufacturing Guidance for Active Pharmaceutical Ingredients
FDA (September 1998)	Investigating Out-of-Specification Test Results for Pharmaceutical Production

**Figure 1: Laboratory Investigation for OOS Results**

It is critical to implement the procedure and document that it has been followed and completed. Should the investigation go beyond the laboratory, it must be timely, in-depth, objective, conclusive and well-documented. The investigation review process should not be cumbersome or time-consuming.

During the investigation of a suspect lot or batch, two key issues must be addressed:

- What to do with the suspect lot or batch during the investigation
- What to do with related lots or batches, both completed and in-process, during the investigation

In general, these investigations require personnel who are independent and well-trained, and who should be held accountable for their performance. Investigators need adequate time to perform their assessment while the suspect lot or batch is quarantined and all new production is potentially placed on hold. Investigators can and should seek support from all areas that can contribute to the probe (e.g., pharmaceutical development, QA, technical services, laboratory and production). To ensure sufficient resources, consideration should be given to having a dedicated group to conduct all investigations.

The investigator needs to determine whether the event was an isolated incident or was related to other batches, products or systems. The conclusions of the investigation need to be definitive. If the outcome is to accept the batch, there must be a high degree of confidence that the entire batch meets all acceptance criteria and that the systems used to manufacture and test the batch are in control. Finally, a conclusion needs to be made concerning any impact on validation.

## Out-of-Specification Results

A laboratory investigation should be initiated **immediately** to determine if a laboratory error is the cause of an OOS result (**Figure 1**) or if the result is representative of the batch (**Figure 2**). The investigation may have one of the following outcomes:

- If the initial investigation indicates that the laboratory results are valid, the investigation focuses on the batch (**Figure 2**).
- If the laboratory results are invalid, the invalid results are not reported; however, the rationale for this conclusion must be clearly documented, and the invalid results must be maintained in the investigation file. The sample can be retested to obtain valid results to use in the assessment of the batch.
- If the laboratory investigation is inconclusive, consideration should be given for another analyst, in addition to/or instead of the original analyst, to perform any retesting. A sample of a standard or previous batch of known activity, as well as the original sample, should be included in the testing.

The following are important points for an investigation of an OOS result:

- An OOS result should be immediately brought to the attention of the laboratory supervisor so that events and activities can be quickly documented while test solutions are still available and useable for subsequent retesting.
- The solutions, glassware and samples that the analyst used must be retained until the investigation is completed.
- Production and QA should be notified to conduct a formal investigation of batch processing, unless the preliminary

laboratory investigation has clearly demonstrated that a laboratory/analyst error has occurred and concluded that retesting is the viable scientific option.

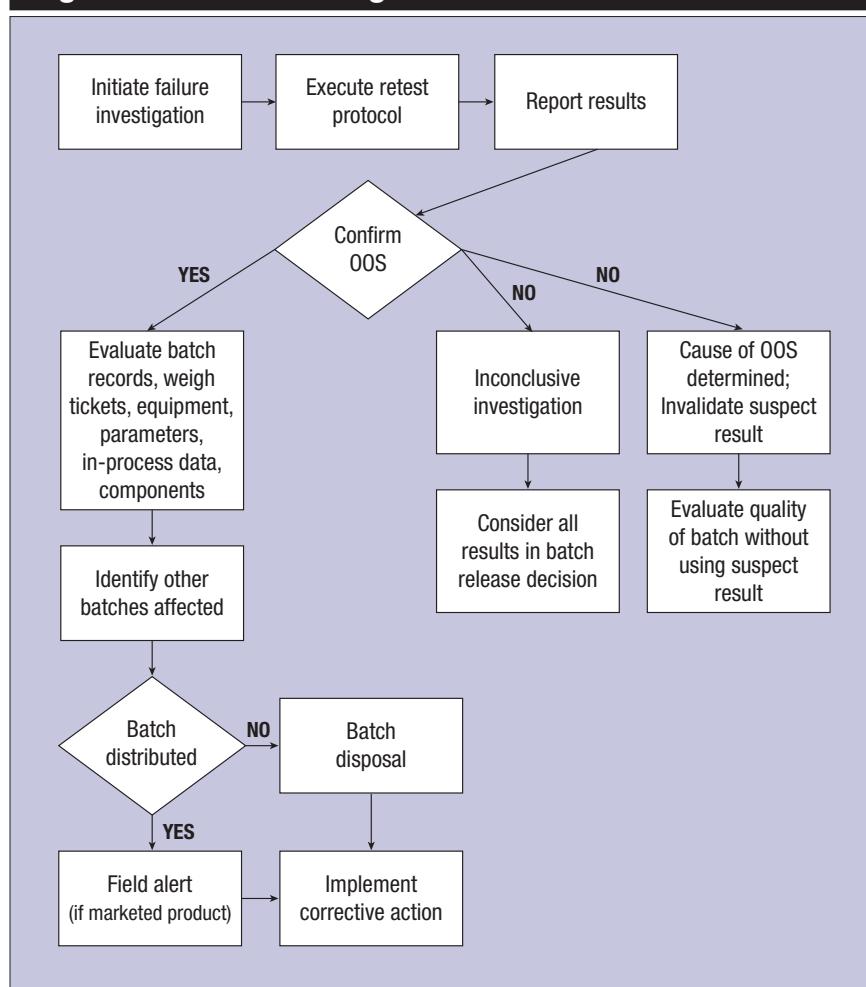
- Resampling should be considered only if there is a valid scientific concern with the integrity of the original sample.
- If retesting is initiated, at least four retests are conducted followed by a decision on the batch. The final decision must be approved by QA.
- Any vendor laboratory should review the Draft Guidance: *Investigating OOS Test Results for Pharmaceutical Production*, September 1998.

- Documentation throughout the investigation is of the utmost importance.

## Corrective Action

While discovery of the root cause of the problem should be the expected outcome of any OOS investigation, that may, in reality, be difficult to determine. Inconclusive results need to be documented. Effective corrective actions must be instituted as the result of the OOS investigation. Management must combine the corrective action with good documentation to minimize the occurrence of future problems.

**Figure 2: Failure Investigation for OOS Results**



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## Training

Management must ensure that all personnel associated with the manufacturing and testing process are trained effectively and that the training is documented. The analysts and operators should be trained in performing the tests and in compliance requirements. These employees should review critical SOPs including those for process change, equipment calibration and how to handle OOS results.

## Conclusions

At the conclusion of an OOS investigation, the documentation should be complete. The outcome of an OOS investigation should be that the root cause of the problem has been identified and needed corrective and/or preventive actions have been implemented on a timely basis. Ongoing review and analysis of investigations will help to identify trends and



systemic quality problems, leading to improved quality processes.

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