Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

May 2022

Pharmaceutical Quality/Manufacturing Standards
Current Good Manufacturing Practice (CGMP)

Revision 1

Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production Guidance for Industry

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

May 2022

Pharmaceutical Quality/Manufacturing Standards
Current Good Manufacturing Practice (CGMP)

TABLE OF CONTENTS

Contains Nonbinding Recommendations

Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance for industry provides the Agency's current thinking on how to evaluate out-of-specification (OOS) test results. For purposes of this document, the term *OOS results* includes ***all*** test results that fall outside the specifications or acceptance criteria established in drug applications, drug master files (DMFs), official compendia, or by the manufacturer. The term also applies to all in-process laboratory tests that are outside of established specifications.[2]

This guidance applies to chemistry-based laboratory testing of drugs regulated by CDER. It is directed toward traditional drug testing and release methods. These laboratory tests are performed on active pharmaceutical ingredients, excipients and other components, in-process materials, and finished drug products[3] to the extent that current good manufacturing practice (CGMP) regulations (21 CFR parts 210 and 211) and the Federal Food, Drug, and Cosmetic Act (the Act) (section 501(a)(2)(B)) apply. The principles in this guidance also apply to in-house testing of drug product components that are purchased by a firm. This guidance can also be used by contract firms performing production and/or laboratory testing responsibilities. Specifically, the guidance discusses how to investigate OOS test results, including the responsibilities of laboratory personnel, the laboratory phase of the investigation, additional testing that may be necessary, when to expand the investigation outside the laboratory, and the final evaluation of all test results.

The Agency, in accordance with its August 2002 "Pharmaceutical CGMPs for the 21st Century" initiative, encourages modern approaches to manufacturing, monitoring, and control to enhance

[1] This guidance has been prepared by the Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research (CDER). You may submit comments on this guidance at any time. Submit comments to Docket No. FDA-1998-D-0019 (available at https://www.regulations.gov/docket/FDA-1998-D-0019).

[2] In certain instances, in-process testing is done solely to determine the need for real-time equipment or system adjustments to prevent process drift. This guidance does not address these situations.

[3] Chemistry-based laboratory testing of biotechnology products that are under the jurisdiction of CDER is within the scope of this guidance. While this guidance is not intended to address biological assays (e.g., in vivo, immunoassays) it does briefly discuss Design and Analysis of Biological Assays (USP<111>).

process predictability and efficiency. Process Analytical Technology (PAT) takes a different approach to quality assurance by using process controls and in-process data as the release specification instead of relying on single laboratory determinations to make batch acceptability decisions. This guidance is not intended to address PAT approaches, as routine in-process use of these methods might include other considerations. For information on timely in-process testing, see the CGMP guidance entitled *PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance* (September 2004).

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

Laboratory testing, which is required by the CGMP regulations (§§ 211.160 and 211.165), is necessary to confirm that components, containers and closures, in-process materials, and finished products conform to specifications, including stability specifications.

Testing also supports analytical and process validation efforts.[4] General CGMP regulations covering laboratory operations can be found in part 211, subparts I (Laboratory Controls) and J (Records and Reports). These regulations provide for the establishment of scientifically sound and appropriate specifications, standards, and test procedures that are designed to ensure that components, containers and closures, in-process materials, and finished drug products conform to the established standards. Section 211.165(f) of the CGMP regulations specifies that finished drug products that fail to meet established standards, specifications, or other relevant quality control criteria must be rejected. "will be rejected" から変更

Both finished pharmaceuticals and active pharmaceutical ingredients (APIs) are to be manufactured in accordance with current good manufacturing practice under section 501(a)(2)(B) of the Act. Current good manufacturing practice for APIs includes the performance of scientifically sound raw material testing, in-process monitoring, release and stability testing, process validation, and adequate investigations of any OOS result obtained from such testing. All citations to part 211 in this document pertain to finished pharmaceuticals, but these referenced regulatory requirements are also consistent with Agency guidance on CGMP for APIs with respect to laboratory controls, which include out-of-specification investigations. See FDA's

[4] Specifications must be scientifically sound and appropriate (§ 211.160(b)), test procedures must be validated as to their accuracy, sensitivity, specificity, and reproducibility (§ 211.165(e)), and the suitability of the test procedures under actual conditions of use must be documented (§ 211.194(a)(2)). For products that are the subjects of new drug applications (NDAs), abbreviated new drug applications (ANDAs), or investigational new drug applications (INDs), specifications are contained in the application or DMF. Specifications for nonapplication products may be found in official compendia or established by the manufacturer.

Q7A → Q7

guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (September 2016) (ICH Q7) for specific recommendations.[5]

The responsibility of a contract testing laboratory in meeting these requirements is equivalent to that of a manufacturing firm.

III. IDENTIFYING AND ASSESSING OOS TEST RESULTS — PHASE I: LABORATORY INVESTIGATION

FDA regulations require that an investigation be conducted whenever an OOS test result is obtained (§ 211.192).[6] The purpose of the investigation is to determine the cause of the OOS result. The source of the OOS result should be identified either as an aberration of the measurement process or an aberration of the manufacturing process. Even if a batch is rejected based on an OOS result, the investigation is necessary to determine if the result is associated with other batches of the same drug product or other products. Batch rejection does not negate the need to perform the investigation. The regulations require that a written record of the investigation be made, including the conclusions and follow-up (§ 211.192).

To be meaningful, the investigation should be thorough, timely, unbiased, well-documented, and scientifically sound. The first phase of such an investigation should include an initial assessment of the accuracy of the laboratory's data. Whenever possible, this should be done before test preparations (including the composite or the homogenous source of the aliquot tested) are discarded. This way, hypotheses regarding laboratory error or instrument malfunctions can be tested using the same test preparations. If this initial assessment indicates that no causative errors were made in the analytical method used to arrive at the data, a full-scale OOS investigation should be conducted. For contract laboratories, the laboratory should convey its data, findings, and supporting documentation to the manufacturing firm's quality unit (QU). The manufacturing firm's QU should then initiate the Phase 2 (full-scale) OOS investigation, whenever no clearly causative laboratory error was identified.

A. Responsibility of the Analyst

The first responsibility for achieving accurate laboratory testing results lies with the analyst who is performing the test. The analyst should be aware of potential problems that could occur during the testing process and should watch for problems that could create inaccurate results.

In accordance with the CGMP regulations in § 211.160(b)(4), the analyst should ensure that only those instruments meeting established performance specifications are used and that all instruments are properly calibrated.

[5] We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance page at https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs.

[6] Although the subject of this document is OOS results, much of the guidance may be useful for examining results that are out of trend.

Certain analytical methods have system suitability requirements, and systems not meeting these requirements should not be used. For example, in chromatographic systems, reference standard solutions may be injected at intervals throughout chromatographic runs to measure drift, noise, and repeatability. If reference standard responses indicate that the system is not functioning properly, all of the data collected during the suspect time period should be properly identified and should not be used. The cause of the malfunction should be identified and, if possible, corrected before a decision is made whether to use any data prior to the suspect period.

Analysts should check the data for compliance with test specifications before discarding test preparations or standard preparations. When unexpected results are obtained and no obvious explanation exists, test preparations should be retained, if stable, and the analyst should inform the supervisor. An assessment of the accuracy of the results should be started immediately.

If errors are obvious, such as the spilling of a sample solution or the incomplete transfer of a sample composite, the analyst should immediately document what happened. Analysts should not knowingly continue an analysis they expect to invalidate at a later time for an assignable cause (i.e., analyses should not be completed for the sole purpose of seeing what results can be obtained when obvious errors are known).

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 result. Data should be assessed promptly to ascertain if the results might 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 test 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 met quality control specifications.

6. Evaluate the performance of the test 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.

OOS test results should not be attributed to analytical error without completing an investigation that clearly establishes a laboratory root cause. Both the initial laboratory assessment and the following OOS investigation should be documented fully.

IV. INVESTIGATING OOS TEST RESULTS — PHASE II: FULL-SCALE OOS INVESTIGATION

When the initial assessment does not determine that laboratory error caused the OOS result and testing results appear to be accurate, a full-scale OOS investigation using a predefined procedure should be conducted. The objective of such an investigation should be to identify the root cause of the OOS result and take appropriate corrective action and preventive action.[7] A full-scale investigation should include a review of production and sampling procedures and will often include additional laboratory testing. Such investigations should be given the highest priority. Among the elements of this phase is evaluation of the impact of OOS result(s) on already distributed batches.

A. Review of Production

The investigation should be conducted by the QU and should involve all other departments that could be implicated, including manufacturing, process development, maintenance, and engineering. In cases where manufacturing occurs off-site (i.e., performed by a contract manufacturer or at multiple manufacturing sites), all sites potentially involved should be included in the investigation. Other potential problems should be identified and investigated.

The records and documentation of the manufacturing process should be fully reviewed to determine the possible cause of the OOS result(s).

A full-scale OOS investigation should consist of a timely, thorough, and well-documented review. A written record of the review should include the following information.

1. A clear statement of the reason for the investigation.

2. A summary of the aspects of the manufacturing process that may have caused the problem.

3. The results of a documentation review, with the assignment of actual or probable cause.

4. The results of a review made to determine if the problem has occurred previously.

5. A description of corrective actions taken.

[7] Please note that § 211.192 requires a thorough investigation of any discrepancy, including documentation of conclusions and follow-up. Implicit in this requirement for investigation is the need to implement corrective actions and preventive actions. Corrective action and preventive action are consistent with the principles in ICH guidance for industry *Q10 Pharmaceutical Quality System* (April 2009).

If this part of the OOS investigation confirms the OOS result and is successful in identifying its root cause, the OOS investigation may be terminated and the product rejected. However, a failure investigation that extends to other batches or products that may have been associated with the specific failure must be completed (§ 211.192). If any material was reprocessed after additional testing, the investigation should include comments and the signatures of appropriate personnel, including production and QU personnel.

OOS results may indicate a flaw in product or process design. For example, a lack of robustness in product formulation, inadequate raw material characterization or control, substantial variation introduced by one or more unit operations of the manufacturing process, or a combination of these factors can be the cause of inconsistent product quality. In such cases, it is essential that redesign of the product or process be undertaken to ensure reproducible product quality.[8]

B. Additional Laboratory Testing

A full-scale OOS investigation may include additional laboratory testing beyond the testing performed in Phase I. These include (1) retesting a portion of the original sample and (2) resampling.

1. Retesting

Part of the investigation may involve retesting of a portion of the original sample. The sample used for the retesting should be taken from the same homogeneous material that was originally collected from the lot, tested, and yielded the OOS results. For a liquid, it may be from the original unit liquid product or composite of the liquid product; for a solid, it may be an additional weighing from the same sample composite prepared for the original test.

Situations where retesting is indicated include investigating testing instrument malfunctions or to identify a possible sample handling problem, for example, a suspected dilution error. Decisions to retest should be based on the objectives of the testing and sound scientific judgment. It is often important for the predefined retesting plan to include retests performed by an analyst other than the one who performed the original test. A second analyst performing a retest should be at least as experienced and qualified in the method as the original analyst.

The CGMP regulations require the establishment of specifications, standards, sampling plans, test procedures, and other laboratory control mechanisms (§ 211.160).

FDA inspections have revealed that some firms use a strategy of repeated testing until a passing result is obtained, then disregarding the OOS results without scientific justification. This practice of "testing into compliance" is unscientific and objectionable under CGMP. The maximum number of retests to be performed on a sample should be

[8] OOS results might also be the result of the objectionable practice of making unauthorized or unvalidated changes to the manufacturing process.

specified in advance in a written standard operating procedure (SOP). The number may vary depending upon the variability of the particular test method employed, but should be based on scientifically sound principles. The number of retests should not be adjusted depending on the results obtained. The firm's predetermined retesting procedures should contain a point at which the additional testing ends and the batch is evaluated. If the results are unsatisfactory at this point, the batch is suspect and must be rejected or held pending further investigation (§ 211.165(f)). Any deviation from this SOP should be rare and done in accordance with § 211.160(a), which states that any deviations from written specifications, sampling plans, test procedures, or other laboratory control mechanisms shall be recorded and justified. In such cases, before starting additional retesting, a protocol should be prepared (subject to approval by the QU) that describes the additional testing to be performed and specifies the scientific and/or technical handling of the data.

In the case of a clearly identified laboratory error, the retest results would substitute for the original test result. However, all original data must be retained (§ 211.180) and an explanation should be recorded.[9] This record should be initialed and dated by the involved persons and include a discussion of the error and supervisory comments. (See section III of this guidance for more details on a laboratory investigation.)

If no laboratory or calculation errors are identified in the first test, there is no scientific basis for invalidating initial OOS results in favor of passing retest results. All test results, both passing and suspect, should be reported[10] and considered in batch release decisions.

2. Resampling

While retesting refers to analysis of the original, homogenous sample material, resampling involves analyzing a specimen from any additional units collected as part of the original sampling procedure or from a new sample collected from the batch, should that be necessary.

The original sample from a batch should be sufficiently large to accommodate additional testing in the event an OOS result is obtained. In some situations, however, it may be appropriate to collect a new sample from the batch. Control mechanisms for examination of additional specimens should be in accordance with predetermined procedures and sampling strategies (§ 211.165(c)).

When all data have been evaluated, an investigation might conclude that the original sample was prepared improperly and was therefore not representative of the batch quality (§ 211.160(b)(3)). Improper sample preparation might be indicated, for example, by widely varied results obtained from several aliquots of an original composite (after determining there was no error in the performance of the analysis). Resampling should be performed by the same qualified, validated methods that were used for the initial

[9] See §§ 211.68 and 211.188. See also FDA guidance for industry *Data Integrity and Compliance With Drug CGMP* (December 2018).

[10] In other words, all data are reported in, for example, quality control reports, batch records, Certificates of Analysis, in accordance with §§ 211.188 and 211.192.

sample. However, if the investigation determines that the initial sampling method was inherently inadequate, a new accurate sampling method must be developed, documented, and reviewed and approved by the QU (§§ 211.160 and 211.165(c)).

C. Reporting Testing Results

Practices used in reporting and interpretation of test results include (1) averaging and (2) outlier tests.

1. Averaging

There are both appropriate and inappropriate uses of averaging test data during original testing and during an OOS investigation:

a. Appropriate uses

Averaging data can be a valid approach, but its use depends upon the sample and its purpose. For example, in an optical rotation test, several discrete measurements are averaged to determine the optical rotation for a sample, and this average is reported as the test result. If the sample can be assumed to be homogeneous, (i.e., an individual sample preparation designed to be homogenous), using averages can provide a more accurate result. In the case of microbiological assays, the U.S. Pharmacopeia (USP) prefers the use of averages because of the innate variability of the biological test system.

It should be noted that a test might consist of a specific number of replicates to arrive at a result. For instance, an HPLC assay result may be determined by averaging the peak responses from a number of consecutive, replicate injections from the same preparation (usually 2 or 3). The assay result would be calculated using the peak response average. This determination is considered one test and one result.[11] This is a distinct difference from the analysis of different portions from a lot, intended to determine variability within the lot, and from multiple full analyses of the same homogenous sample. The use of replicates to arrive at a single reportable[12] result, and the specific number of replicates used, should be specified in the written, test method approved by the QU. Acceptance limits for variability among the replicates should also be specified in the method. Unexpected variation in replicate determinations should trigger remedial action as required by § 211.160(b)(4). If acceptance limits for replicate variability are not met, the test results should not be used.

In some cases, a series of complete tests (full run-throughs of the test procedure), such as assays, are part of the test method. It may be appropriate to specify in the test method that the average of these multiple assays is considered one test and represents one reportable result. In this case, limits on acceptable variability among the individual assay

[11] See section V.B Cautions for further clarification.

[12] The term *reportable result* as used in this document means a final analytical result. This result is appropriately defined in the written approved test method and derived from one full execution of that method, starting from the original sample.

results should be based on the known variability of the method and should also be specified in the test methodology.[13] A set of assay results not meeting these limits should not be used.

These appropriate uses of averaging test data should be used during an OOS investigation only if they were used during the original testing that produced the OOS result.

b. Inappropriate uses

Reliance on averaging has the disadvantage of hiding variability among individual test results. For this reason, all individual test results should normally be reported as separate values. Where averaging of separate tests is appropriately specified by the test method, a single averaged result can be reported as the final test result. In some cases, a statistical treatment of the variability of results is reported. For example, in a test for dosage form content uniformity, the standard deviation (or relative standard deviation) is reported with the individual unit dose test results.

Averaging can also conceal variations in different portions of a batch, or within a sample. For example, the use of averages is inappropriate when performing powder blend/mixture uniformity or dosage form content uniformity determinations. In these cases, testing is intended to measure variability within the product, and individual results provide the information for such an evaluation.

In the context of additional testing performed during an OOS investigation, averaging the result(s) of the original test that prompted the investigation with additional retest or resample results obtained during the OOS investigation is not appropriate because it hides variability among the individual results. Relying on averages of such data can be particularly misleading when some of the results are OOS and others are within specifications. It is critical that the laboratory provide all individual results for evaluation and consideration by the QU, which is responsible for approving or rejecting, e.g., drug products, in-process materials (§ 211.22).

For example, in an assay of a finished drug with a specification of 90 to 110 percent, an initial OOS result of 89 percent followed by additional retest results of 90 percent and 91 percent would produce an average of 90 percent. While this average would meet specification,[14] the additional test results also tend to confirm the original OOS result. However, in another situation with the same specifications, an initial OOS result of 80 percent followed by additional test results of 85 percent and 105 percent would also produce an average of 90 percent but present a much different picture. These results do not confirm the original OOS result but show high variability and may not be reliable. In both examples, the individual results, not the average, should be used to evaluate the quality of the product.

[13] See footnote 11.

[14] When arriving at a batch disposition decision, it is important for a firm to assess whether the low assay value may project to a subpotency failure before the product's labeled expiration date.

2. Outlier Tests

The CGMP regulations require that statistically valid quality control criteria include appropriate acceptance and/or rejection levels (§ 211.165(d)). On rare occasions, a value may be obtained that is markedly different from the others in a series obtained using a validated method. Such a value may qualify as a statistical outlier. An outlier may result from a deviation from prescribed test methods, or it may be the result of variability in the sample. It should never be assumed that the reason for an outlier is error in the testing procedure, rather than inherent variability in the sample being tested.

Outlier testing is a statistical procedure for identifying from an array those data that are extreme. The possible use of outlier tests should be determined in advance. This should be written into SOPs for data interpretation and be well documented. The SOPs should include the specific outlier test to be applied with relevant parameters specified in advance. The SOPs should specify the minimum number of results required to obtain a statistically significant assessment from the specified outlier test.

(旦) イタリック体の引用表現をやめて USP<111> とだけ

For biological assays having a high variability, an outlier test may be an appropriate statistical analysis to identify those results that are statistically extreme observations. The USP describes outlier tests in the general chapter on Design and Analysis of Biological Assays (USP<111>). In these cases, the outlier observation is omitted from calculations. The USP also states that "arbitrary rejection or retention of an apparently aberrant response can be a serious source of bias…the rejection of observations solely on the basis of their relative magnitudes, without investigation as to cause, is a procedure to be used sparingly" (USP <111>).

(旦) 追加「原因について調査せずに」とより解りやすい説明

For validated chemical tests with relatively small variance, and if the sample being tested can be considered homogeneous (for example, an assay of a composite of a dosage form drug to determine strength), an outlier test is only a statistical analysis of the data obtained from testing and retesting. It will not identify the cause of an extreme observation and, therefore, should not be used to invalidate the suspect result. Occasionally, an outlier test may be of some value in understanding how discordant from a data set a result is, but can be used solely in an informational capacity in the course of an investigation to determine the distance of a result from the mean.[15]

(旦) "estimating" を「補助的に使用」 "used in auxiliary fashion" → "understanding" 「理解」と単独では情報として20%の設定の調査で使用できる

Outlier tests have no applicability in cases where the variability in the product is what is being assessed, such as for content uniformity, dissolution, or release rate determinations. In these applications, a value perceived to be an outlier may in fact be an accurate result of a nonuniform product.

When using these practices during the additional testing performed in an OOS investigation, the laboratory will obtain multiple results. It is again critical for the laboratory to provide all test results for evaluation and consideration by the QU in its

[15] Outlier testing should not be used to invalidate chemical assays. See United States District Court for the District of New Jersey, U.S.A. v. Barr Laboratories, Inc., et al. Civil Action Number 92-1744, OPINION, February 4, 1993.

final disposition decision. In addition, when investigation by a contract laboratory[16] does not determine an assignable cause, all test results should be reported to the customer on the certificate of analysis.

V. CONCLUDING THE INVESTIGATION

To conclude the investigation, the results should be evaluated, the batch quality should be determined, and a release decision should be made by the QU. The relevant SOPs should be followed in arriving at this point. Once a batch has been rejected, there is no limit to further testing to determine the cause of the failure so that a corrective action can be taken.

A. Interpretation of Investigation Results

The QU is responsible for interpreting the results of the investigation. An initial OOS result does not necessarily mean the subject batch fails and must be rejected. The OOS result should be investigated, and the findings of the investigation, including retest results, should be interpreted to evaluate the batch and reach a decision regarding release or rejection (§ 211.165).

In those instances where an investigation has revealed a cause, and the suspect result is invalidated, the result should not be used to evaluate the quality of the batch or lot. Invalidation of a discrete test result may be done only upon the observation and documentation of a test event that can reasonably be determined to have caused the OOS result.

In those cases where the investigation indicates an OOS result is caused by a factor affecting the batch quality (i.e., an OOS result is confirmed), the result should be used in evaluating the quality of the batch or lot. A confirmed OOS result indicates that the batch does not meet established standards or specifications and should result in the batch's rejection, in accordance with § 211.165(f), and proper disposition. For inconclusive investigations — in cases where an investigation (1) does not reveal a cause for the OOS test result and (2) does not confirm the OOS result — the OOS result should be given full consideration in the batch or lot disposition decision.

In the first case (OOS confirmed), the investigation changes from an OOS investigation into a batch failure investigation, which must be extended to other batches or products that may have been associated with the specific failure (§ 211.192).

In the second case (inconclusive), the QU might still ultimately decide to release the batch. For example, a firm might consider release of the product under the following scenario:

A product has an acceptable composite assay range of 90.0 to 110.0 percent. The initial (OOS) assay result is 89.5 percent. Subsequent sample preparations from the original sample yield the following retest results: 99.0, 98.9, 99.0, 99.1, 98.8, 99.1, and 99.0 percent. A comprehensive laboratory investigation (Phase 1) fails to reveal any laboratory error. Review of events during

[16] The Agency also recommends that OOS investigation reports be provided to the customer.

production of the batch reveals no aberrations or indication of unusual process variation.[17] Review of the manufacturing process and product history demonstrates that the process is robust. The seven passing retest results are all well within the known limits of variability of the method used. Batch results from in-process monitoring, content uniformity, dissolution, and other tests are consistent with the passing retest results. After a thorough investigation, a firm's QU might conclude that the initial OOS result did not reflect the true quality of the batch.

It is noteworthy in this scenario that the original, thorough laboratory investigation failed to find any assignable cause. However, if subsequent investigation nonetheless concludes that the source of the OOS result was a cause unrelated to the manufacturing process, in response to this atypical failure to detect the laboratory deviation, it is essential that the investigation include appropriate follow-up and scrutiny to prevent recurrence of the laboratory error(s) that could have led to the OOS result.

As the above example illustrates, any decision to release a batch, in spite of an initial OOS result that has not been invalidated, should come only after a full investigation has shown that the OOS result does not reflect the quality of the batch. In making such a decision, the QU should always err on the side of caution.

B. Cautions

1. Averaging results from multiple sample preparations from the original sample

In cases where a series of assay results (intended to produce a single reportable result) are required by the test procedure and some of the individual results are OOS, some are within specification, and all are within the known variability of the method, the passing results are no more likely to represent the true value for the sample than the OOS results. For this reason, a firm should err on the side of caution and treat the average of these values as an OOS result, even if that average is within specification. This approach is consistent with the principle outlined in the USP General Notices that an official article shall comply with the compendial standard any time a compendial test is applied.[18] Thus, every individual application of the official test should be expected to produce a result that meets specifications.

2. Averaging results from same final sample preparation

As noted in the Averaging section (IV.C.1.), there may be cases where the test method specifies appropriate acceptance criteria for variability and a pre-defined number of replicates from the final diluted sample solution to arrive at a result. For example, an HPLC test method may specify both acceptance criteria for variability and that a single reportable result be determined by averaging the peak response from a number of consecutive, replicate injections from the same

[17] As an example, evaluation of process variation would determine if established equipment, facility, and process control limits were met.

[18] USP, *General Notices*, Section 7.10, "Test Results, Statistics, and Standards" states "Analytical results observed in the laboratory (or calculated from experimental measurements) are compared with stated acceptance criteria to determine whether the article conforms to compendial requirements."

test vial. In these cases, and given the acceptance criteria for variability are met, the result of any individual replicate in and of itself should not cause the reportable result to be OOS.

3. Borderline results that are within specification

An assay result that is low, but within specifications, should also raise a concern. One cause of the result could be that the batch was not formulated properly. Batches must be formulated with the intent to provide not less than 100 percent of the labeled or established amount of active ingredient (§ 211.101(a)). This would also be a situation where the analytical result meets specifications, but caution should be used in the release or reject decision.[19]

As with all analytical testing conducted to evaluate the quality of a drug, all records pertaining to the OOS test result should be retained. Records must be kept of complete data derived from all tests performed to ensure compliance with established specifications and standards (§ 211.194).

C. Field Alert Reports

旧とは表現の違いのみ。旧はラフな書き方だった。

For those products that are the subject of an approved new drug application or abbreviated new drug application, regulations require submitting within 3 working days a field alert report (FAR) of information concerning any failure of a distributed batch to meet any of the specifications established in an application (21 CFR 314.81(b)(1)(ii)).[20] OOS test results on these products are considered to be one kind of "information concerning any failure" described in this regulation. Unless the OOS result on the distributed batch is found to be invalid within 3 days, an initial FAR should be submitted. A follow-up FAR should be submitted when the OOS investigation is completed.

[19] As noted in the ICH guidance for industry *Q1E Evaluation of Stability Data* (2004), "[i]f the assay value of a batch is lower than 100 percent of label claim at the time of batch release, it might fall below the lower acceptance criterion before the end of the proposed shelf life." Appropriate actions must be taken if testing results indicate that a batch may fall below assay specifications prior to its expiration date (see § 211.137 and 211.165).

[20] See FDA guidance for industry *Field Alert Report Submission Questions and Answers* (July 2021).