DRAFT GUIDELINES
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GUIDANCE FOR INDUSTRY

OUT-OF-SPECIFICATION TEST RESULTS

Draft - Not for Implementation

'...An **Out-of-Specification** Test Result is not necessary a product failure - and needs to be qualified ...

FDA's NEW OOS GUIDANCE

GUIDANCE FOR INDUSTRY
Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production.

I. INTRODUCTION

This guidance has been prepared by the Office of Compliance / Division of Manufacturing and Product [1] Quality, Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on evaluating OOS test results. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

This guidance for industry provides the Agency's current thinking on how to evaluate suspect, or out of specification (OOS), test results.

For purposes of this document, the term *OOS results* includes ***all*** suspect results that fall outside the specifications or acceptance criteria established in new drug applications, official compendia, or by the manufacturer.

This guidance applies to laboratory testing during the manufacture of active pharmaceutical ingredients, excipients, and other components and the testing of finished products to the extent that current good manufacturing practices (CGMP) regulations apply (21 CFR parts 210 and 211). Specifically, the guidance discusses how to investigate suspect, or 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.

TABLE OF CONTENTS

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

II. BACKGROUND

FDA considers the integrity of laboratory testing and documentation records to be important during drug manufacturing. Laboratory testing, which is required by the cGMP regulations (§ 211.165), is necessary to confirm that components, containers-closures, in-process materials; finished products, conform to specifications, including stability.

Testing also supports analytical and process validation efforts. 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 and containers of drug products conform to the established standards. Section 211.165(f) of the CGMP regulations specifies that products that fail to meet established standards and other relevant quality control criteria will be rejected.

III. IDENTIFYING AND ASSESSING OOS TEST RESULTS

FDA regulations require that an investigation be conducted whenever an OOS test result is obtained. The purpose of the investigation is to determine the cause of the OOS. 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.

Every Failure (OOS) MUST be investigated and its impacts on related batches evaluated

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 of the investigation and follow-up (211.192).

To be meaningful, the investigation should be thorough, timely, unbiased, well-documented, and scientifically defensible.

The first phase of the investigation includes an initial assessment of the accuracy of the laboratory's data, ***before*** test solutions are discarded, whenever possible.

Investigate, Conclude and Follow-up Every Specification Failure

This way, hypotheses regarding laboratory error or instrument malfunctions may be tested using the same test solutions. If this initial assessment indicates that no errors were made in the analytical process used to arrive at the data, a complete failure investigation should follow.

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 OOS results.

In accordance with the CGMP regulations[1] the analyst should ensure that only those instruments meeting established specifications are used and that all instruments are properly calibrated. [1](§ 211.160 (b)(4)),

Certain analytical methods have system suitability requirements, and systems not meeting such 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.

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

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 corrected before a decision is made whether to use any data prior to the suspect period.

Track Analytical Failures Back to Their Origin Point

Before discarding test preparations or standard preparations, analysts should check the data for compliance with specifications. When unexpected results are obtained and no obvious explanation exists, test preparations should be retained 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.

Analysis Developing a Fault MUST be Stopped Immediately

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). These same responsibilities extend to analysts at contract testing laboratories.

B. Responsibilities of the 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 may be attributed to laboratory error, or whether the results could indicate problems in the manufacturing process.

Is the OOS a Laboratory or Production Error?

An immediate assessment could include re-examination of the actual solutions, test units, and glassware used in the original measurements and preparations, which would allow more credibility to be given to laboratory error theories.

Steps should be taken as part of the supervisor's assessment:

Key:- [**D E C I D E D**]

[1]. **D**iscuss the test method with the analyst; confirm analyst knowledge of and performance of the correct procedure.

[2]. **E**xamine the raw data obtained in the analysis, including chromatograms and spectra, and identify anomalous or suspect information.

[3]. **C**onfirm the performance of the instruments.

[4]. **D**etermine that the appropriate reference standards, solvents, reagents, and other solutions were used and that they meet quality control specifications.

[5]. **E**valuate the performance of the testing method to ensure that it is performing according to the standard expected based on method validation data.

[6]. **D**ocument and preserve evidence of this 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) can be tested. Examination of the retained solutions can be performed as part of the laboratory investigation.

Examples:

Solutions can be re-injected as part

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

of an investigation where a transient equipment malfunction is suspected.

This could occur, if bubbles were introduced during an injection on a chromatographic system, which other tests indicated was performing properly. Such theories are difficult to prove.

However, a re-injection 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 forms, where possible, examination of the dosage unit tested might determine whether it was damaged 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 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 (i.e. the extraction procedure).

It is important that each step in the investigation be fully documented. The supervisor should ascertain not only the reliability of the individual value obtained, but also the significance these OOS results represent in the overall quality assurance program.
Supervisors should be especially alert to developing trends.

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 ensure that it does not occur again.

To ensure full compliance with the CGMP regulations, the manufacturer also should maintain adequate documentation of the corrective action.

OOS Rules:
Clear Error- Invalidate
Unclear Failure - Investigate
Do not assume anything!

In summary, when clear evidence of laboratory error exists, laboratory testing results should be invalidated. When evidence of laboratory error remains unclear, a failure investigation should be conducted to determine what caused the unexpected results.

It should not be assumed that failing test results are attributable to analytical error without performing and documenting an investigation. Both the initial laboratory assessment and the following failure investigation should be documented fully.

IV. INVESTIGATING OOS TEST RESULTS

Full scale investigations

When the initial assessment does not determine that laboratory error caused the OOS result and testing results appear to be accurate, a full-scale failure investigation using a predefined procedure should be conducted.

The objective of such an investigation should be to identify the source of the OOS result. Varying test results could indicate problems in the manufacturing process, or result from sampling problems.
Such investigations present a challenge both to employees and to management and should be given the highest priority.

The investigation should be conducted by the quality control unit and should involve all other

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

departments that could be implicated, including manufacturing, process development, maintenance, and engineering. Other potential problems should be identified and investigated.

QC Unit Investigates: Production and Laboratory Systems & Documentation

The records and documentation of the manufacturing process should be fully investigated to determine the possible cause of the OOS results.

[A]. General Investigational Principles

A failure investigation should consist of a timely, thorough, and well-documented review.

The written record should reflect that the following general steps have been taken. [**I - T R A C**]

[1]. The reason for the **I**nvestigation has been clearly identified.
[2]. **T**he overall manufacturing process sequences that may have caused the problem should be summarized.
[3]. **R**esults of the documentation review should be provided with the assignment of actual or probable cause.
[4]. **A** review should be made to determine if the problem has occurred previously.
[5]. **C**orrective actions taken should be described.

The general review should include a list of other batches and products possibly affected and any required corrective actions taken including any comments and signatures of appropriate production and quality control personnel regarding any material that may have been reprocessed after additional testing.

[B]. Laboratory Phase of an Investigation

A number of practices are used during the laboratory phase of an investigation. These include:

[1]. Retesting a portion of the original sample
[2]. Testing a specimen from the collection of a new sample from the batch
[3]. Re-sampling testing data
[4]. Using outlier testing.

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 that had been prepared by the analyst.

Situations where retesting is indicated include investigating testing instrument malfunctions or to identify a possible sample handling integrity problem, for example, a suspected dilution error. Generally, retesting is neither specified nor prohibited by approved applications or by the compendia.

Investigation Retesting: First Performed on the original sample by a Second Analyst

Decisions to retest should be based on the objectives of the testing and sound scientific judgement. Retesting should be performed by an analyst other than the one who performed the original test.

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

The establishment of such control mechanisms for examination of additional specimens for commercial

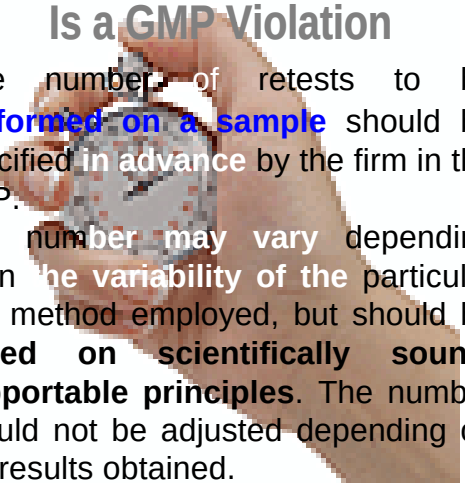
ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

or regulatory compliance testing must be in accordance with "predetermined guidelines or sampling strategies"

(USP 23, General Notices and Requirements, p.9).

Some firms have used a strategy of repeated testing until a passing result is obtained (testing into compliance), then disregarding the OOS results without scientific justification. Testing into compliance is objectionable under the CGMPs.

Multiple Retesting: Into Compliance Is a GMP Violation



The number of retests to be performed on a sample should be specified in advance by the firm in the SOP.

The number may vary depending upon the variability of the particular test method employed, but should be **based on scientifically sound, supportable principles**. The number should not be adjusted depending on the results obtained.

The firm's predetermined testing procedures should contain a point at which the testing ends and the product is evaluated. If, at this point, the results are unsatisfactory, the batch is suspect and must be rejected or held pending further investigation (§ 211.165(f)).

In the case of a clearly identified laboratory error, the retest results would substitute for the original test results. The original results should be retained, however, and an explanation recorded.

This record should be initialed and dated by the involved persons and include a discussion of the error and supervisory comments.

If no laboratory or statistical 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 and considered in batch release decisions.

Consider OOS + Retest Result - if the Investigated OOS can not be Invalidated

2. RE-SAMPLING

While retesting refers to analysis of the original sample, re-sampling involves analyzing a specimen from the collection of a new sample from the batch. The establishment of control mechanisms for examination of additional specimens for commercial or regulatory compliance testing should be in accordance with predetermined procedures and sampling strategies (§ 211.165(c)).

In some cases, when all data have been examined, it may be concluded that the original sample was prepared improperly and was therefore not representative of the batch (§ 211.160(b)(3)).

Re-sample Only if Original Sample is Proved as Unrepresentative

A re-sampling of the batch should be conducted if the investigation shows that the original sample was not representative of the batch.

This would be indicated, for example, by widely varied results obtained from several aliquots of the original composite (after determining there was no error in the performance of the analysis).

Re-sampling should be performed by the same qualified, validated methods that were used for the initial sample.

However, if the investigation determines that the initial sampling method was in error, a new accurate sampling method must be developed,

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

qualified, and documented. (§§ 211.160 and 165(c)).

3. AVERAGING

Averaging test 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 homogeneous), using averages can provide a more accurate result.

In the case of microbiological assays, the USP prefers the use of averages because of the innate variability of the biological test system.

Reliance on averages has the disadvantage of hiding variability among individual test results. For this reason, unless averaging is specified by the test method or adequate written investigation procedures, **all individual test results should be reported**.

In some cases, a statistical treatment of the variability of results should be reported. For example, in a test for dosage form content uniformity, the standard deviation (or relative standard deviation) is also reported.

Averaging also can conceal variations in the different portions of the sample. For example, the use of averages is inappropriate when performing powder blend/mixture uniformity or dosage form content uniformity determinations.

In these cases, the testing is intended to measure variability within the product, and the individual results should be reported.

It should be noted that a test might consist 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. This is a distinct difference from the analysis of different portions from a lot, intended to determine variability within the lot.

The use of replicates should be included in the written, approved, test methodology. Unexpected variation in replicate determinations should trigger investigation and documentation requirements (21 CFR 211.192).

In some cases, a series of assay results may be a part of the test procedure. If some of the results are OOS and some are within specification and all are within the documented variation of the method, the passing results should be given no more credence than the failing results, in the absence of documented evidence that analytical error had occurred.

Relying on test data averaging in such a case can be particularly misleading. For example, in an assay with a given range of 90 to 110 percent, test results of 89 percent, 89 percent, and 92 percent would produce an average of 90 percent even though two of the assay values represent failing results.

To use averaged results for assay reporting, all test results should conform to specifications. Although the above average of 90 percent may be useful in terms of an overall assessment of process capabilities, the individual assay results indicate non-conformance because two of the three results are outside of the range.

A low assay value should also trigger concerns that the batch was not formulated properly because the batch

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

must be formulated with the intent to provide not less than 100 percent of the labeled or established amount of active ingredient (21 CFR 211.101(a)).

The above example does not necessarily require the manufacturer to fail the batch, but indicates that an immediate investigation should be conducted for batch disposition decisions.

4. 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.

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 section on '*Design and Analysis of Biological Assays'* (USP 23, p. 1705). 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 is a procedure to be used sparingly" (USP 23, p. 1705).

For validated chemical tests with relatively small variance, and if the sample being tested can be considered homogeneous (for example, an assay of composited dosage form 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, thus should not be used to invalidate the data.

An outlier test may be useful as part of the evaluation of the significance of that result for batch evaluation, along with other data.

Don't Use Outlier Testing in Dissolution Content Uniformity (i.e. where variability exists)

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 non-uniform product.

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. The 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

An OOS result does not necessarily mean the subject batch fails and must be rejected.

OOS Results Do Not Automatically Fail the Batch (investigate & interpret fully)

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 used to evaluate the quality of the batch or lot.

A *proven* invalid result is always discarded

Invalidation of a discrete test result is 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 disposal.

For inconclusive investigations i.e. 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 retained in the record and given full consideration in the batch or lot disposition decision.

A un*proven* OOS result is always included

Statistical treatments of data should not be used to invalidate a discrete chemical test result.

In very rare occasions and only after a full investigation has failed to reveal the cause of the OOS result, a statistical analysis may be valuable as one assessment of the probability of the OOS result as discordant, and for providing perspective on the result in the overall evaluation of batch quality

Records must be kept of complete data derived from all tests performed to ensure compliance with established specifications/standards (21 CFR 211.194).

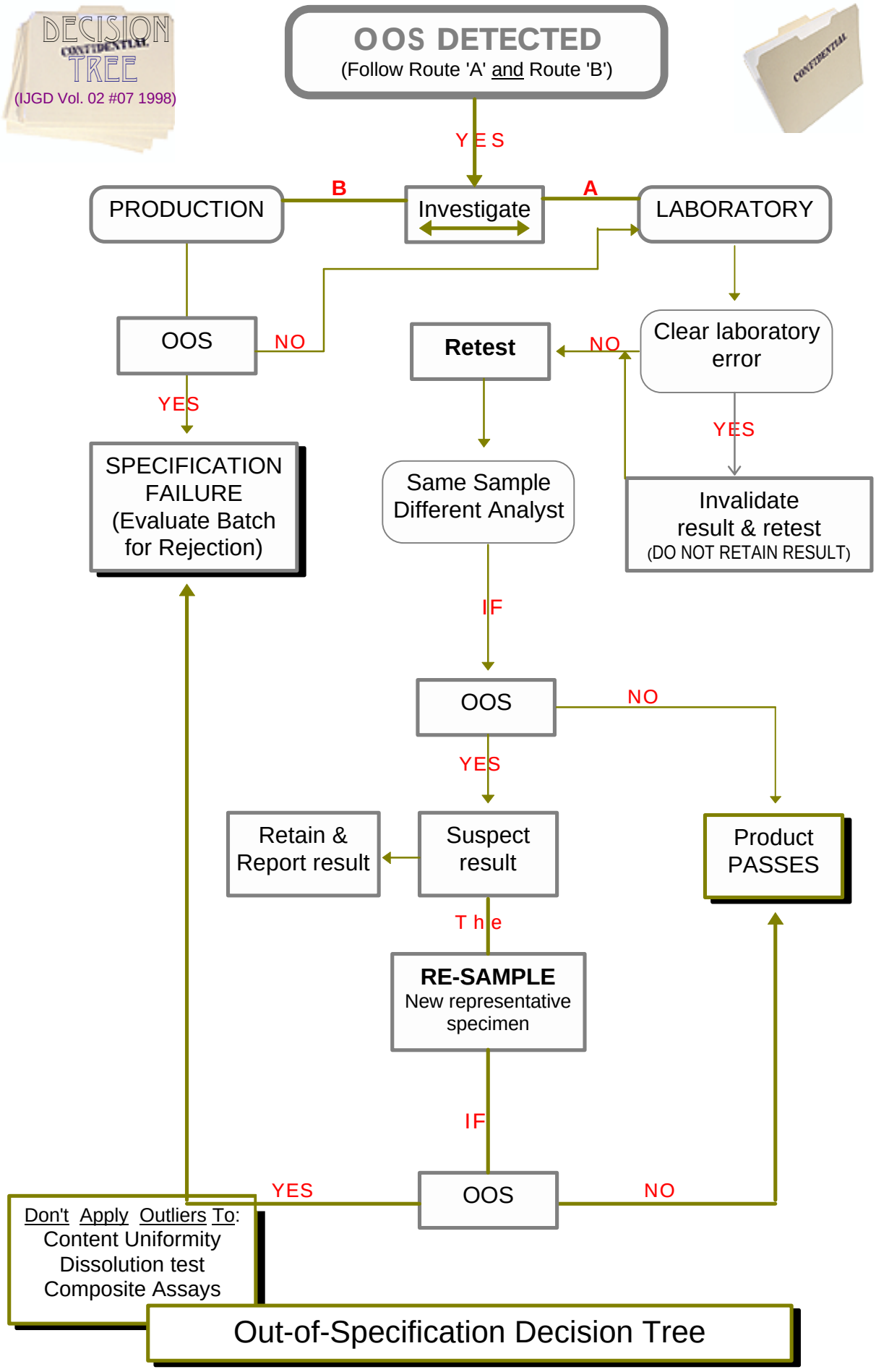
[B]. Reporting

For those products that are the subject of applications, regulations require submitting within three 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).

OOS test results not invalidated on distributed batches/lots for this class of products are considered to be one kind of “information concerning any failure” described in this regulation.

This includes OOS results that are considered to be discordant and of low value in batch quality evaluation. In these cases, a FAR should be submitted.

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim



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