PROCEDURES FOR HANDLING OOS RESULTS

1. PURPOSE

The purpose of this Standard Operation Procedure is to establish a procedure for the routine handling of out-of-specification (OOS) laboratory results The investigation or 'failure investigation' should where ever possible identify the cause of the OOS and evaluate its impact.

2. RESPONSIBILITY

Each Analyst or Researcher is responsible for the immediate analytical review of OOS results in cooperation with the laboratory head of supervisor/delegate. All solutions and standards must be preserved and properly stored.
The laboratory head of supervisor is responsible for the final decision as to the disposition and use of the result.

3. FREQUENCY

Immediately afterwards (where possible) or within 1 to 2 days of each completed analytical test (after being checked, audited and reviewed by the supervisor).

4. PROCEDURE

[a]. **A**nalysts may classify Out-of-Specification Test Results (OOS) as reversible or as non-reversible due to either a :-

- genuine laboratory error or
- sampling error

Non-reversible classification may cover:-

- manufacturing or processing errors (including manufacturing operator error)

[b.] **I**nvestigation for Genuine Laboratory Analytical Error.
Analysts must investigate for laboratory errors which can occur when analysts make analytical mistakes. Check if samples were incorrectly prepared, diluted, injected or stored at inappropriate environmental temperatures or that containers not properly closed or possibly not sampled in the correct designated sampling container.

[e.] **S**uspected laboratory error must be investigated and if a genuine error is found, then the OOS result must immediately be invalidated. The OOS result must be disregarded (after appropriate recording and filing).

[c]. **E**ach Analyst shall review for completeness the entire test procedure, equipment / calibration and calculation used in obtaining the test result using the attached guideline checklists.

[d]. **T**he supervisor shall review and discuss in depth with the analyst, the execution of the entire analytical testing procedure, equipment and calculation used.

[e.] **O**nce the nature of the OOS has been identified - as an laboratory error - a repeat test *must* be performed and the initial test totally discarded as a reversible laboratory error. (since the initial test result was proven invalid)

[f.] **T**he analytical or analyst error must be thoroughly documented and properly invalidated - with written *reasons,* together with the supervisor and analyst *signatures* and *date* of the invalidation process.

INCONCLUSIVE ERRORS RETEST

[g.] **A**n inconclusive error is an OOS where the 'supervisor-analyst investigation' did not draw a firm conclusion and the reason for the error was not clearly identified.

[h.] **R**etest with new aliquot (replicates, if required) from the *same sample,* if the sampling procedure was *proven* OK by investigation.

[i.] **I**f the sampling procedure is found to be in error, then re-sample the target material is undertaken and a new duplicate analysis is performed.

DECISION TREE

5. LIMITATION

[j.] **A**n overview of Out-of-Specification Results procedures is provided by a decision tree flowchart. The decision tree provides a logical set of procedural steps in order to standardize the investigative procedure for all analysts when performing an OOS investigation.

[f.] **R**e-sampling the material for a new representative sample should take place only when the original procedure was found to be clearly non-representative of the whole.

6. DOCUMENTATION

[k.] Out-of-specification (OOS) Test Results Report or ‘failure investigation Test Result Report’ is prepared and filed.

[End of Document]

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➢CHECKLIST➢

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OUT-of-SPECIFICATION RESULTS

'…Averaging passing and OOS Test Results together is not permitted as it conceals the full analytical picture…'

IDENTIFYING OOS TEST RESULTS	
1. Does the firms have a clear SOP spelling out the procedure and investigations required when ever an OOS result is obtained?	❑Yes ❑No
2. Are all firm's 'rejected batch' OOS results investigated as well?	❑Yes ❑No
3. Are the previous (or related) batches associated with the failed batch specification reviewed and the overall impact (on quality) evaluated?	❑Yes ❑No
4. Are *written* investigations undertaken and then follow-up procedures recommended in writing?	❑Yes ❑No
5. Are the investigations performed in a timely manner and follow a defensible scientific logic (see attached Decision Tree)?	❑Yes ❑No
6. Does the companies 'Investigation SOP' include the three key tenants i.e. TO INVESTIGATE - TO CONCLUDE - TO FOLLOW-UP?	❑Yes ❑No
7. Have the laboratory analysts been instructed to keep the original 'suspect test solutions' for possible reanalysis (Ref. Decision Tree)?	❑Yes ❑No
8. When an OOS has been detected does the initial review, before the investigation, check for instrument or system suitability malfunction, faulty reagents, calculation, documentation or transcribing errors?	❑Yes ❑No
9. If no clear analytical errors are detected in a 'suspect result' does a comprehensive 'failure investigation' ALWAYS follow?	❑Yes ❑No
10. Where malfunctions are identified and detected are all prior 'suspect data' evaluated and reviewed for a possible related (or similar) errors?	❑Yes ❑No
11. Are analytical failures tracked *back* to their original point of failure?	❑Yes ❑No
12. When a faulty lab procedure is detected, is the analytical test procedure immediately terminated (as a matter of routine)?	❑Yes ❑No
13. Have the analysts been trained to immediately report to their supervisors an obvious error or an analytical fault?	❑Yes ❑No
14. Are obvious errors (spilling, incorrect dilution, injection volume etc.) documented in the lab book and a brand new test restarted?	❑Yes ❑No

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➢CHECKLIST➢

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OUT-of-SPECIFICATION RESULTS

'…failure investigations are conducted to determine what caused the unexpected OOS result…'

INVESTIGATING OOS TEST RESULTS	
15. Does the supervisor's **'initial assessment'** follow a written in-house 'SOP **procedure '**?	❑Yes ❑No
16. Are the retained 'suspect' sample preparations examined during the **'initial assessment'** and then retested promptly on initiating the **'failure investigation'?**	❑Yes ❑No
17. Where a clear error is identified, is the result immediately invalidated?	❑Yes ❑No
18.Where clear error is NOT identified, is a failure investigation conducted immediately?	❑Yes ❑No
19. Is the firm's full scale failure investigation fully predefined in writing?	❑Yes ❑No
20. Does the firm's own QC Unit perform the 'full scale failure investigation'?	❑Yes ❑No
21. Does the general review include a list of related batches which may be impacted?	❑Yes ❑No
22. Does the full scale failure investigation include the production side and the laboratory side?	❑Yes ❑No
23. Does the laboratory protocol include the two key steps - retesting the original sample *and* testing a new sample from the batch lot?	❑Yes ❑No
24. Retesting the original sample with a **new** analyst, is generally the first step after the **'initial assessment'** is completed?	❑Yes ❑No
25. Are the number of re-tests (usually duplicates) specified and not exceeded? Averaging 'original suspect' and retest results is forbidden.	❑Yes ❑No
26. When improperly prepared samples are proven as faulty, then the original test results may be immediately invalidated?	❑Yes ❑No
27. The firm may re-sample when the investigation highlights that the original sample was unrepresentative?	❑Yes ❑No
28. Where the investigation concludes that the sampling method is in error a new sampling method must be developed and qualified?	❑Yes ❑No
29. To prove the original aliquot is faulty, the analyst prepares two additional aliquots and compares the three sets of results?	❑Yes ❑No

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OUT-of-SPECIFICATION RESULTS

'…Batches must be formulated with the intent to provide 100% of the labeled amount…'

AVERAGING IN OOS RESULTS	
30. Averaging results from a standard solution or a test aliquot is acceptable (i.e. averaging replicate results).	❑Yes ❑No
31. Averaging results from microbial count plates are quite acceptable.	❑Yes ❑No
32. Averaging a set of results, where some are OOS is **not** acceptable.	❑Yes ❑No
33. Hiding an OOS result in any average is **not** acceptable.	❑Yes ❑No
34. When the intent is to highlight variability within the product then averaging is **not** acceptable, but RSD (CV) values are generally reported to show statistical significance.	❑Yes ❑No
35. Replicate peak responses whether test or standard should be averages as one result.	❑Yes ❑No
36. Are analysts trained, so not to average passing *and* OOS results together in order to hide the failing results?	❑Yes ❑No
37. Composite assays, require only one assay result and are in fact average assay values, as opposed to individual content uniformity values.	❑Yes ❑No
38.OUTLIER USE IN OOS RESULTS	
39. Where 'control' and 'specification' lower and upper limits are used in QC criteria an OUTLIER may be outside the control limits but inside the specifications limits? [i.e. an example of OUTLIER use.]	❑Yes ❑No
40. Analyst are trained not to assume OUTLIERS as testing errors but inherent variability in the sample.	❑Yes ❑No
41. The firm has an OUTLIERS SOP detailing the use of OUTLIER TESTS.	❑Yes ❑No
42. OUTLIERS are not permissible in Content Uniformity and Dissolution tests.	❑Yes ❑No
43. Where the intent is to measure the variability, OUTLIERS should not be used.	❑Yes ❑No

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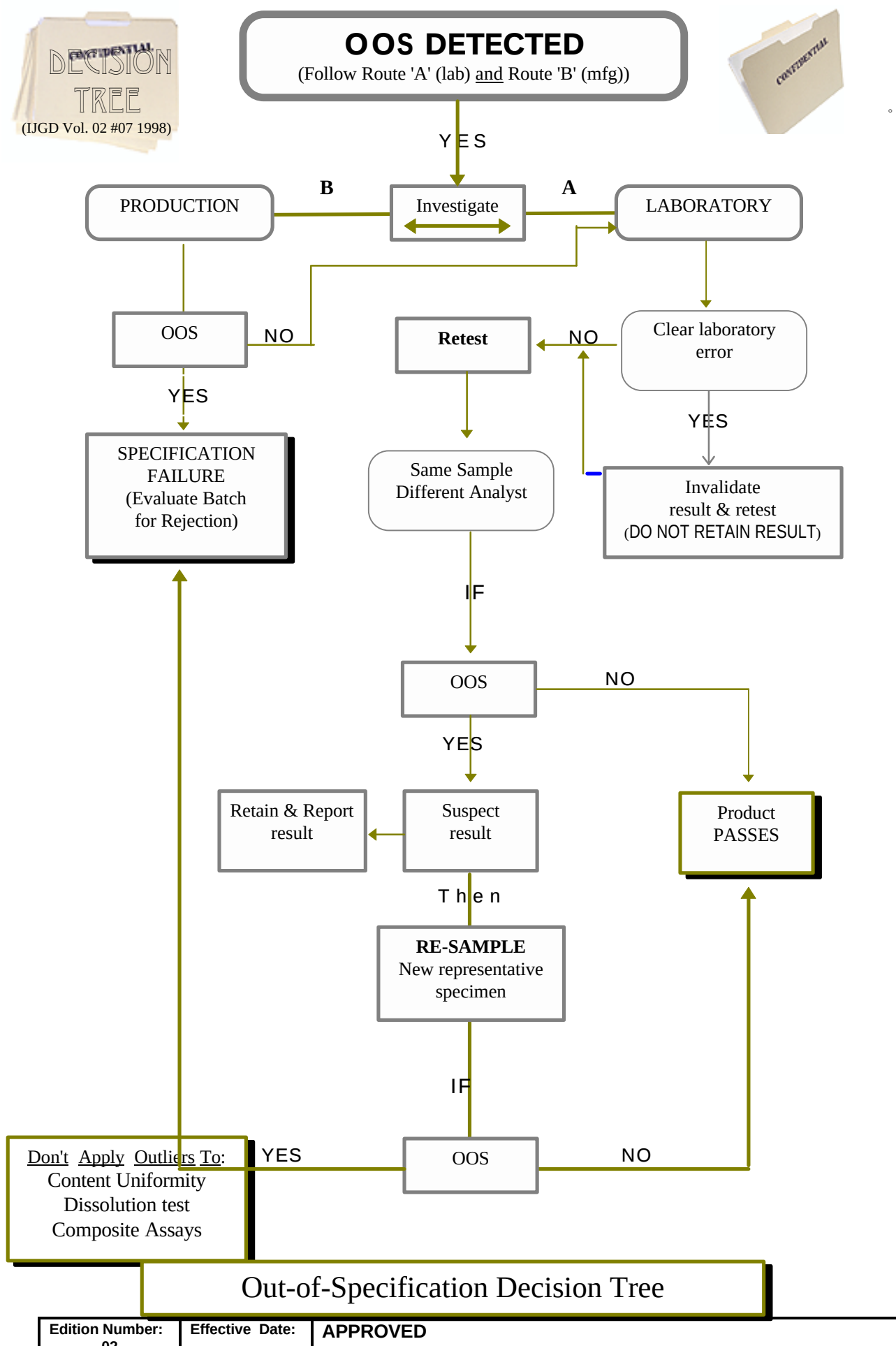

Out-of-Specification Decision Tree

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