RATIONALE

Accurate and reliable analytical results and data are essential for good decision making involving material and product status, stability profile and expiry dating. The establishment of a robust process for checking the veracity of out of specification (OOS) and atypical results and data is vital to this decision making process.

PURPOSE

This guideline provides supporting guidance for handling and investigating OOS or atypical test results in line with GQP 7216 requirements.

SCOPE

This guideline applies to all sites and companies manufacturing products for sale by, or for, GSK. The principles apply to non-manufacturing sites analysing products for distribution.

SUMMARY OF REVISIONS

This guideline has been derived from and supersedes Appendix 5 of the legacy GQMP on Deviation and Non-Conformance Handling dated March 2006.

1. General Principles

The purpose of retesting is to identify and isolate OOS/atypical results.

It is not permissible to do multiple retests as this is likely to influence batch disposition decisions, which is not acceptable. The re-test plan needs to define the point at which testing ends, and a disposition decision is made about any batches involved.

For OOS results obtained during stability testing, it is recognised that doing further testing at the same time-points may not be possible. Under such circumstances, it is advisable to do additional testing at an interim time-point.

Unless there is sound scientific justification to reject the OOS obtained from the original test, both the original results and any results from further testing will be reported with equal weighting. Any sentencing decisions should be made on individual results, and not simply on any calculated mean value.

2. Interpretation of Results

Data can be invalidated immediately for the following reasons:

- The system suitability requirements of the test are not met.
- For multiple measurements of a single sample preparation the raw data is invalidated if the difference between the data is outside of the system precision acceptance criteria. The reason why the system precision was not met needs to be investigated and documented. These are not OOS investigations.
- For multiple sample preparations the corresponding results will be invalidated if the difference between the results is outside of the method precision acceptance criteria. The reason why the method precision was not met needs to be investigated and documented. These are not OOS investigations.

An OOS result should be assessed against any relevant pharmacopoeia or other specifications which contain specific guidance on the procedures to be followed and the acceptance criteria, with respect to further testing and sampling. Examples of tests falling into this category include but are not limited to:

- Content uniformity.
- Dissolution.
- Sterility testing.
- Inspection of packing components.

For example, when conducting United States Pharmacopoeia (USP) dissolution testing, if at Stage S1 one tablet gives a result less than Q+5%, then the test should proceed to Stage S2, in the absence of a demonstrable laboratory error.

If a demonstrable laboratory error in the conduct of the test is noted whilst the test is in progress, then testing needs to be stopped without recourse to the OOS/atypical result handling procedure.

3. Investigation Phases

3.1. Laboratory Investigation Phase

The objective of the laboratory investigation phase is to identify whether there has been a laboratory error, which caused the OOS or atypical result.

The outputs of the laboratory investigation stage should be:

- Decision on validity of test result, i.e. Laboratory error - yes, no or inconclusive.
- Completed Laboratory Investigation Report associated with laboratory investigation.

An inconclusive error is an error which has been suspected, but not proven, to have occurred in the laboratory. Typically, this situation will occur where a result cannot be repeated, (e.g. there is insufficient solution to repeat the measurement, or the test solution has degraded since the time of the original measurement).

A Laboratory Investigation template is available to aid the performing and recording of the laboratory investigation phase.

3.2. Expanded Investigation Phase

The objective of an expanded investigation is to identify the root cause of the OOS/atypical result. The general principle of the re-testing procedure is that there should be more retest results than were generated by the original test. This can be achieved, either by conducting more than one retest, or by increasing the level of replication when conducting the retest.

This phase should include definition of the protocols to be used in conducting an expanded investigation. This should include definition of the following prior to any further laboratory work:

- Any acceptance criteria to be applied during further testing.
- Number of samples/measurements/analysts to be involved.

- Timeframes within which to conduct the investigation.

Consideration should be given to incorporation of the following into the expanded investigation protocols, where possible:

- A second analyst to conduct the testing, using a different instrument.
- Two analysts independently conducting tests.
- A control sample as part of the testing procedure, as long as the lot is expired, or not released to the market, to avoid potential adverse regulatory events.
- A second laboratory, if applicable.

The output of the expanded investigation stage should be an expanded investigation report detailing the results of the investigation, the root cause and any corrective and preventive actions required to address the cause. (see Deviation and Investigation Handling Guideline GQG 6007 for a Toolkit/guide to Conducting Root Cause Investigations).

An Expanded Laboratory Investigation template is to aid the performing and recording of the expanded investigation phase.

4. Time-scales for Investigation Phases

Laboratory Investigation

- The laboratory Investigation should be completed within 2 working days.
- Where testing relates to batches already on the US market, sites need to have the Laboratory Investigation completed within 2 working days.
- Similarly, in Europe, manufacturers must report any quality defect in a medicinal product, which could result in a recall or abnormal restriction on supply.

The time-limit applicable for the completion of the investigation of atypical results is not specifically mandated by regulatory authorities. However, the time limit applied should be the same as that for OOS result investigation. Since the outcome of an investigation into an atypical result may impact the validity of that result and therefore influence how the result of a test is reported, it should be accorded the same importance as an OOS.

The above time-scales relate to the completion of the investigation. It is recognised that separate time-scales will apply to completion of any CAPAs.

5. Review and Approval of Data

All of the data (both original and re-test results) is used in assessing the quality of the batch(es) concerned.

Either:

- All of the individual test results are either assessed against the specification limit.

Or:

- Internal specification limits have been set for individual values, based on historical data for the product concerned, in addition to a limit on the mean value, and the results are assessed against all of these

OOS results cannot be averaged with in specification results. Any decisions should be made on individual results and not just on the calculated mean value alone.

6. Decision Trees

The following decision trees are designed to allow rapid decision-making when investigating OOS results in the laboratory.

Diagram 1

The generic laboratory investigation flowchart (at which a documented oral interview is held between analyst and supervisor). The investigation could include re-measurement/rerunning/re-diluting of the sample for specific scenarios, but otherwise no further laboratory testing is conducted at this stage. The objective is to identify whether there has been a laboratory error, which caused the OOS or atypical result.

Diagram 2

The generic expanded investigation flowchart (a more extensive investigation including production warehousing, engineering, etc., as required). This may include re-sampling from the batch, plus further laboratory testing of additional samples according to a predefined plan.

Diagram 3

The generic additional chromatographic peaks in laboratory investigation testing flowchart.

Diagram 4

The generic stability testing flowchart.

Diagram 5

The blend assays of dry powder inhalers (DPIs) flowchart

Diagram 6

The bulk assay and fine particle mass tests for DPIs flowchart.

Diagram 7

The content uniformity testing of DPIs flowchart

Diagram 8

Microbiological testing flowchart

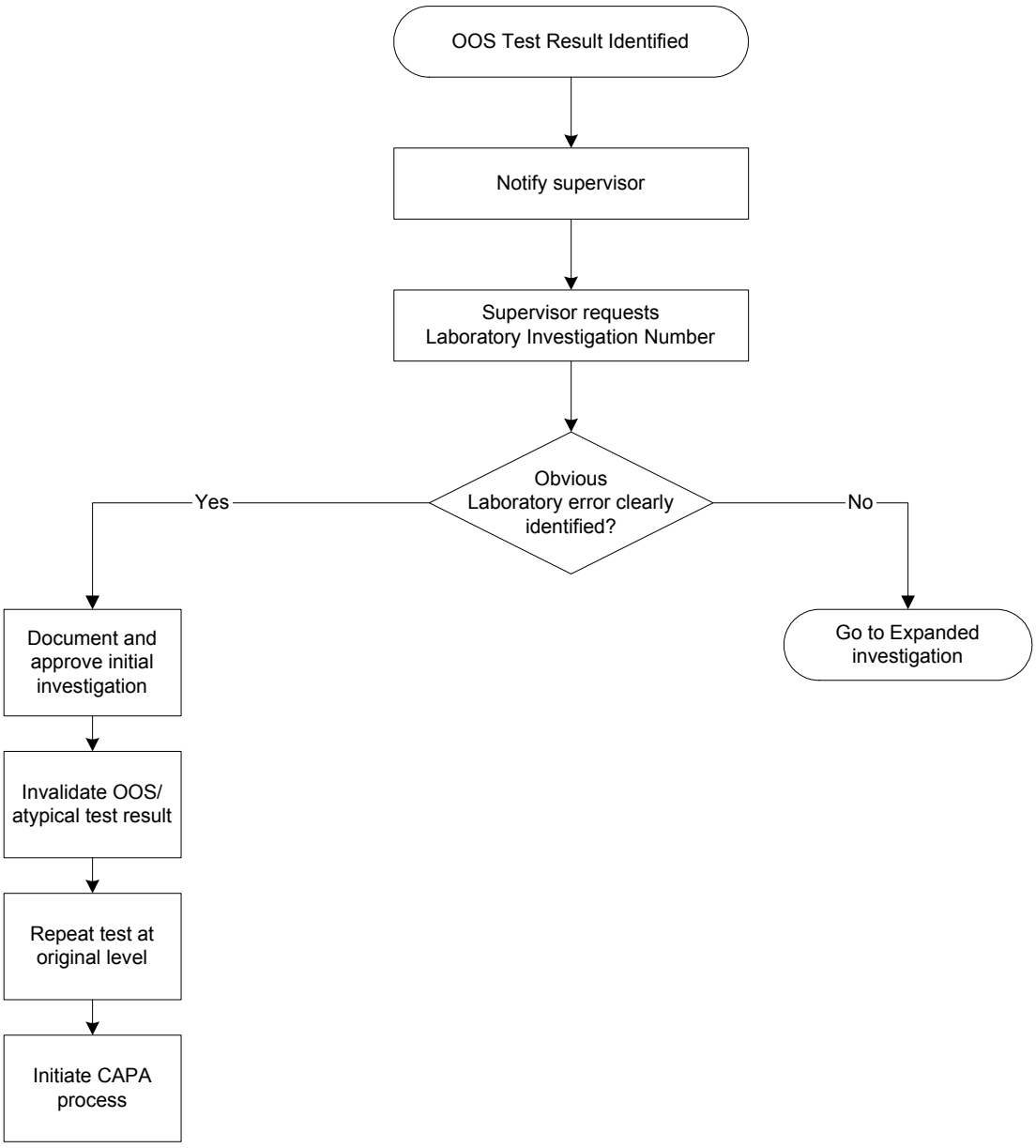
Diagram 9

Microbiological Environmental Monitoring flowchart

Diagram 10

Pictorial Representation of Common Terms

Diagram 1
Generic Laboratory Investigation Flowchart



The original solutions and samples, and any other evidence that may be required to further the investigation, must be retained whenever possible. Retained solutions and samples must be stores under appropriate conditions to ensure stability.

Diagram 2
Generic Expanded Investigation Flowchart

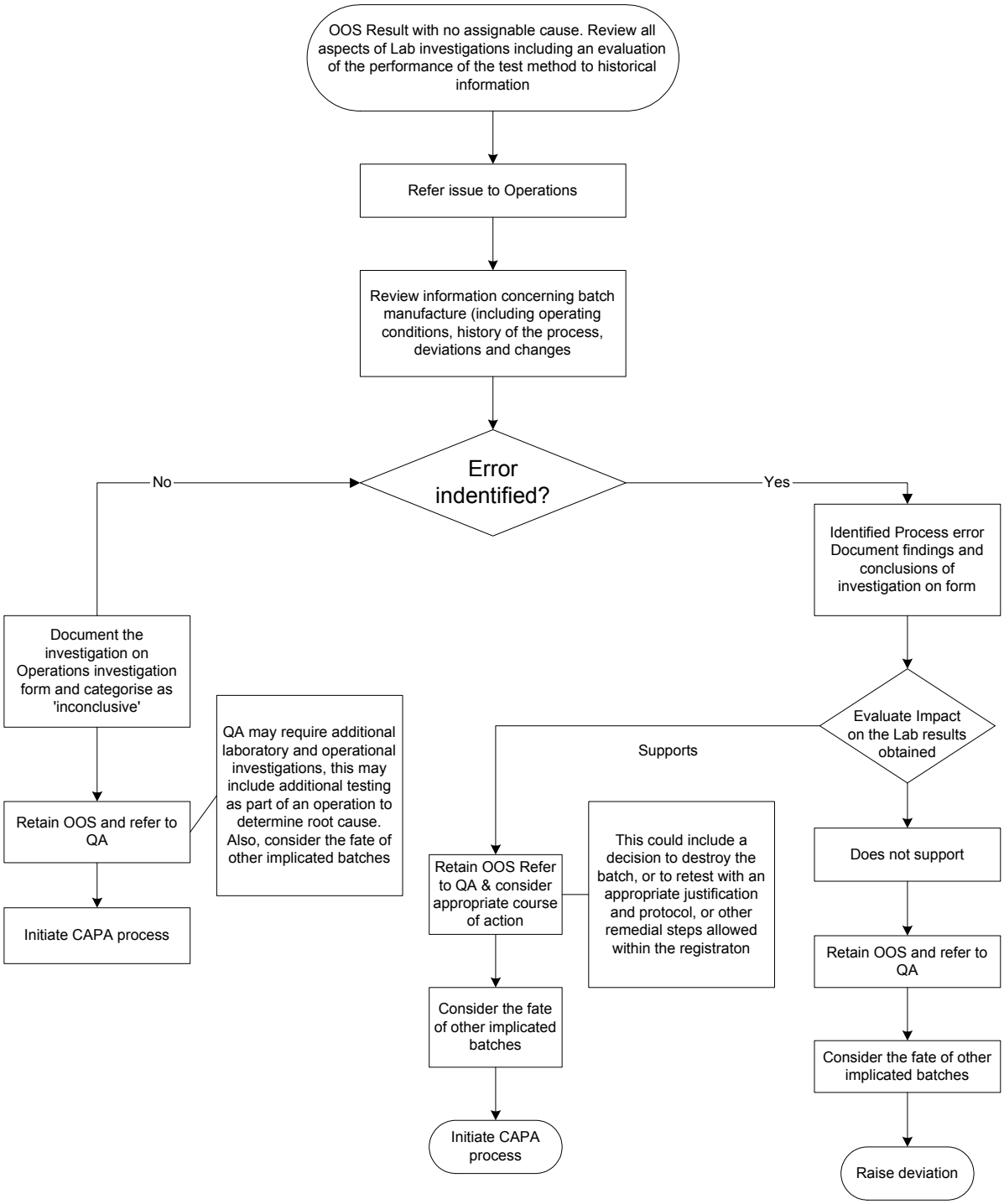


Diagram 3
Generic Additional Chromatographic Peaks in Laboratory Investigation Flowchart

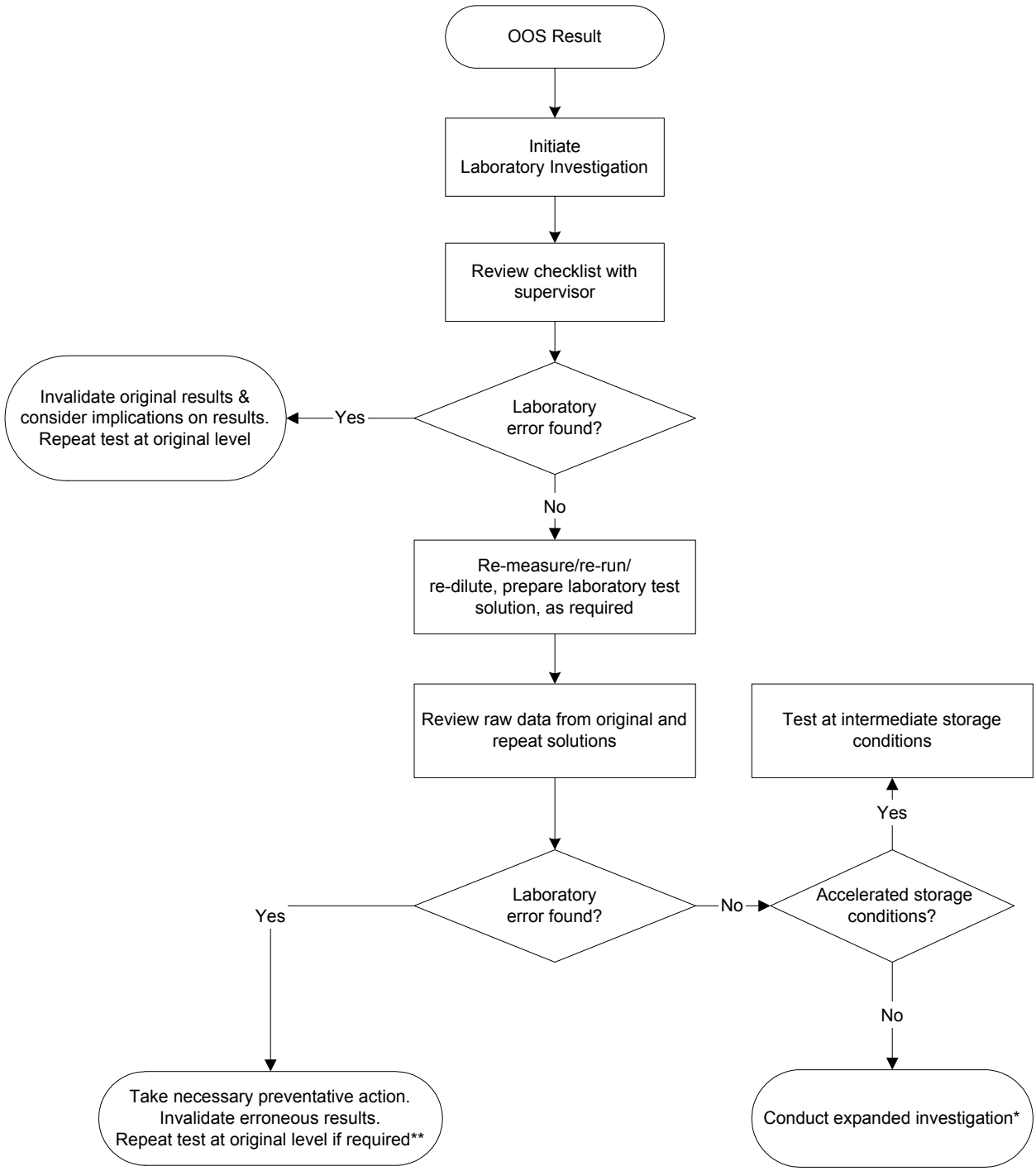
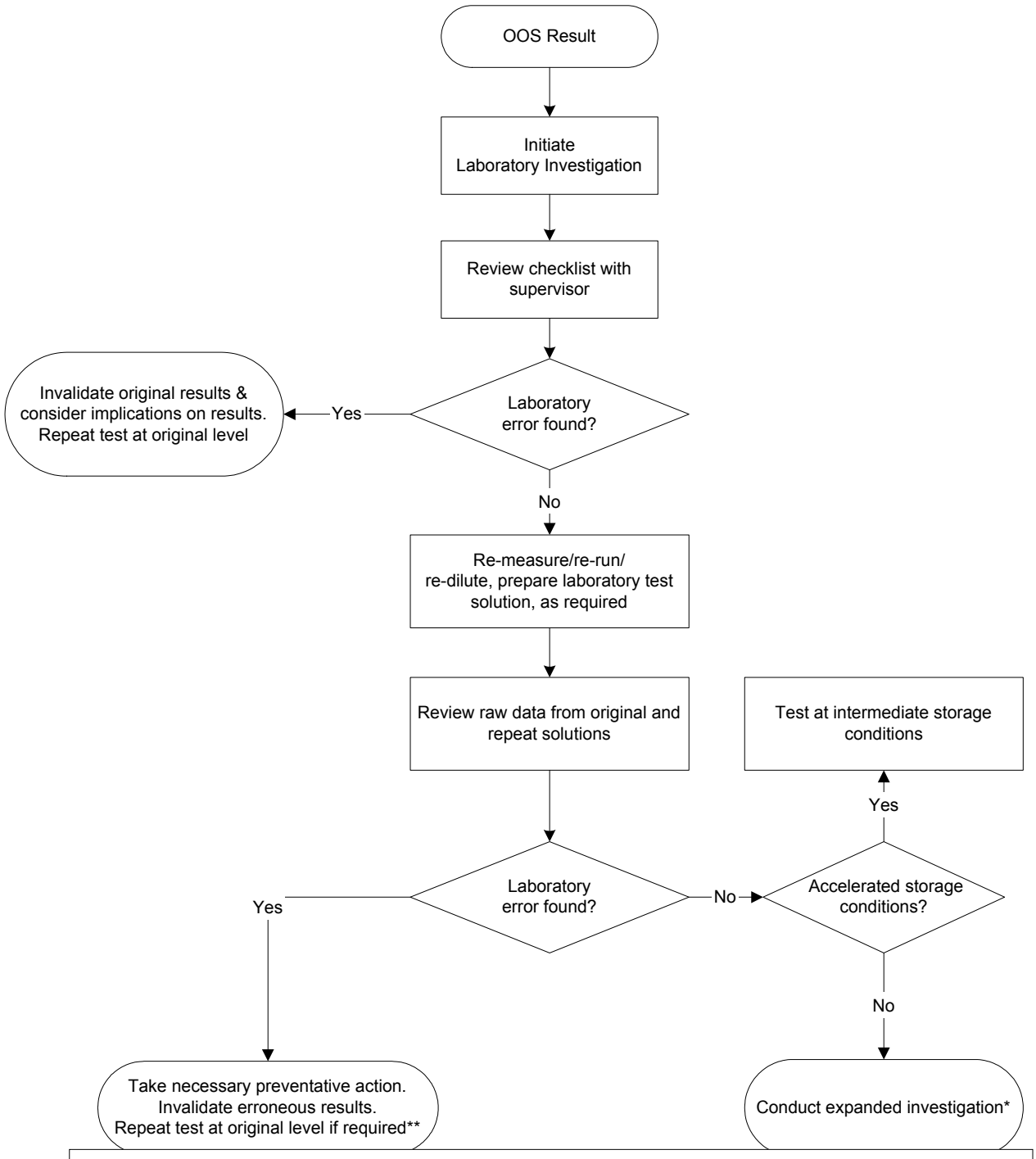


Diagram 4
Generic Stability Testing Flowchart

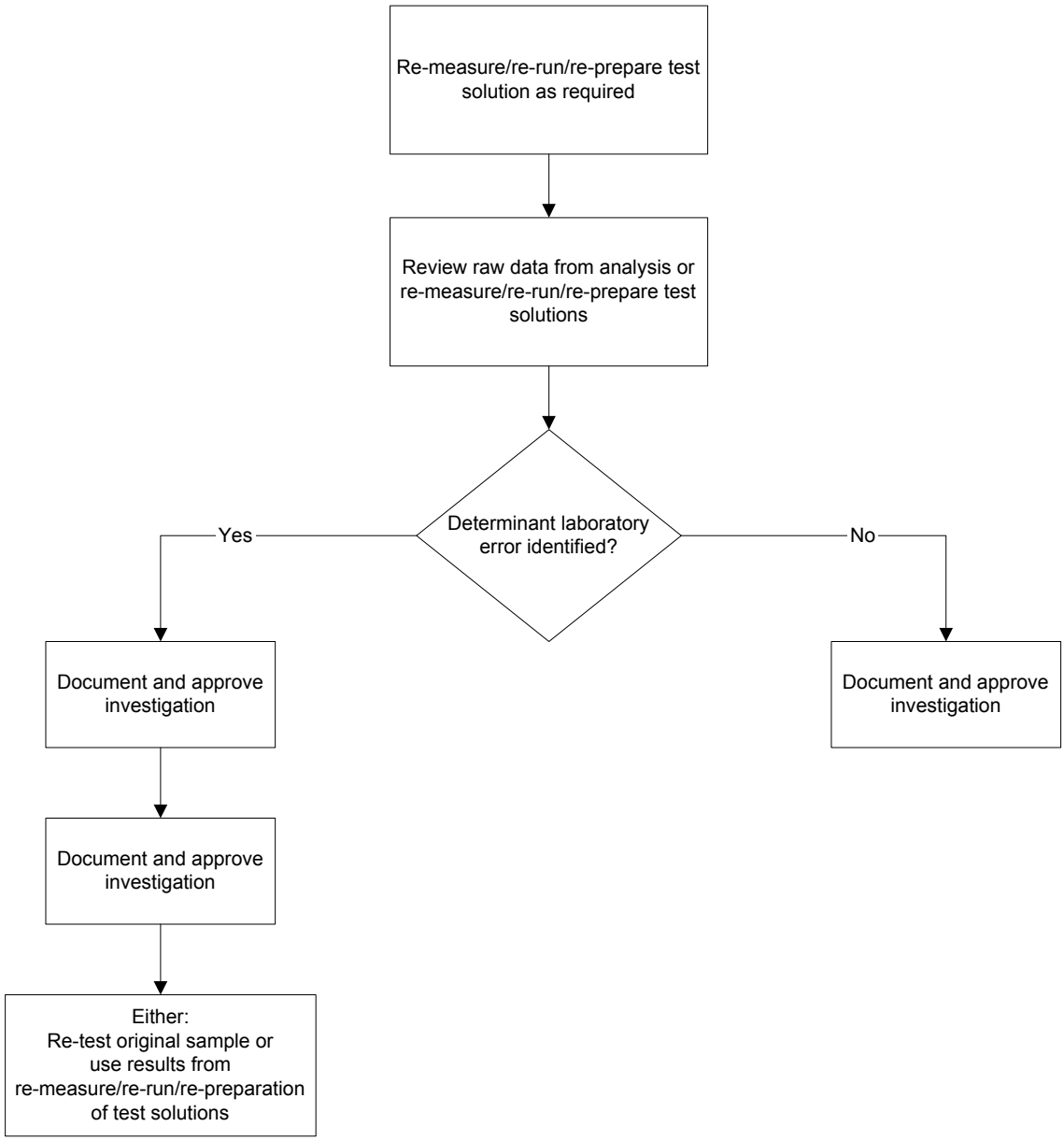


* Many OOS results may be considered to be expected, and form part of a clear trend of results during the life of the stability programme. In such cases, this would negate the necessity to conduct an expanded investigation: the result would be reported in the normal way.

** Reinjection results may be considered valid if a laboratory error is clearly identified that accounts for the original injection.

Diagram 5
Blend Assays of Dry Powder Inhalers (DPI Testing) Flowchart

Diagram 2 - Generic Phase 2 Investigation Flow Chart



The original solutions and samples, and any other evidence that may be required to further the investigation, must be retained whenever possible. Retained solutions and samples must be stored under appropriate conditions to ensure stablility

Diagram 6
Bulk Assay and Fine Particle Mass Tests (DPI Testing) Flowchart

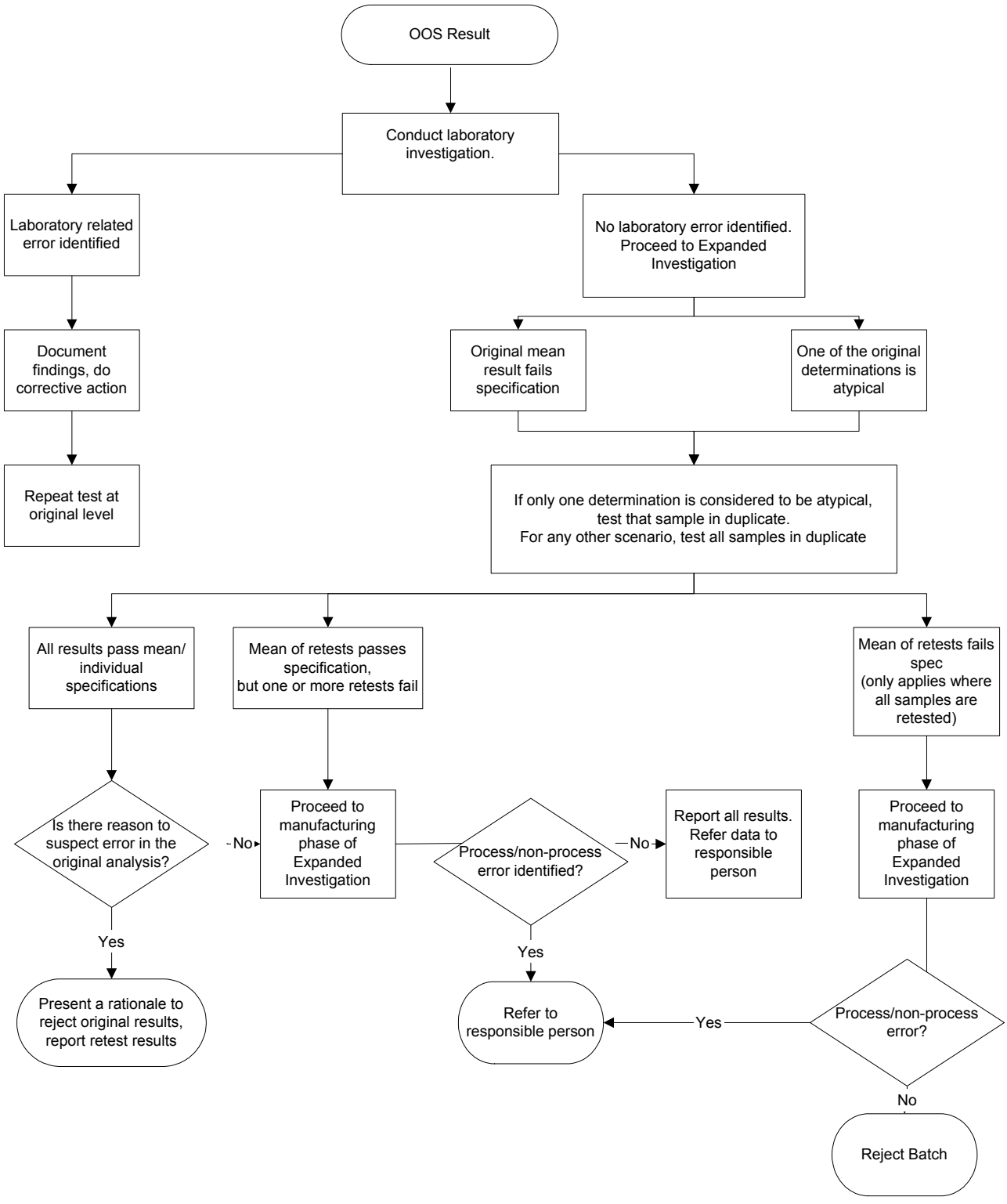


Diagram 7
Content Uniformity Testing (DPI Testing) Flowchart

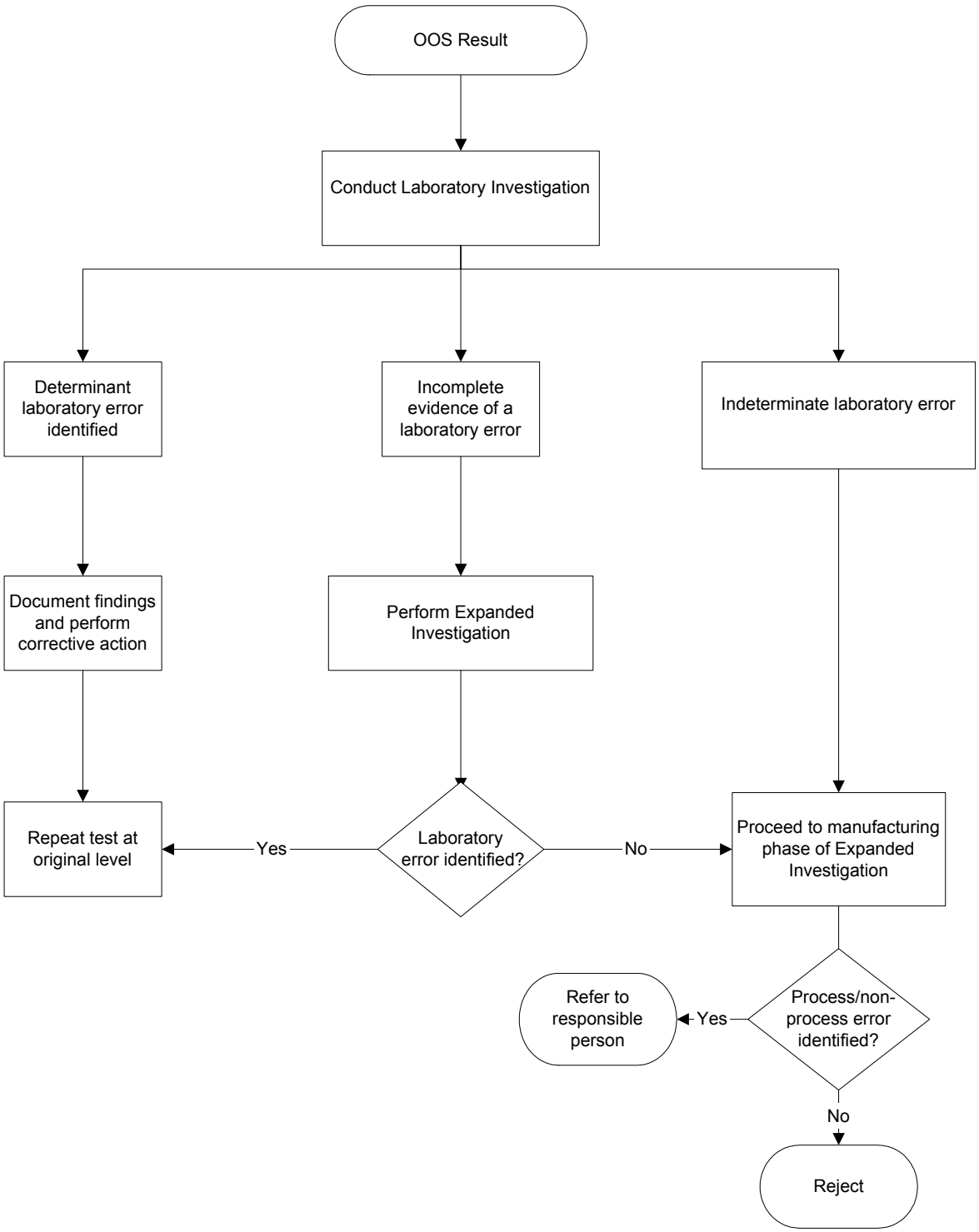
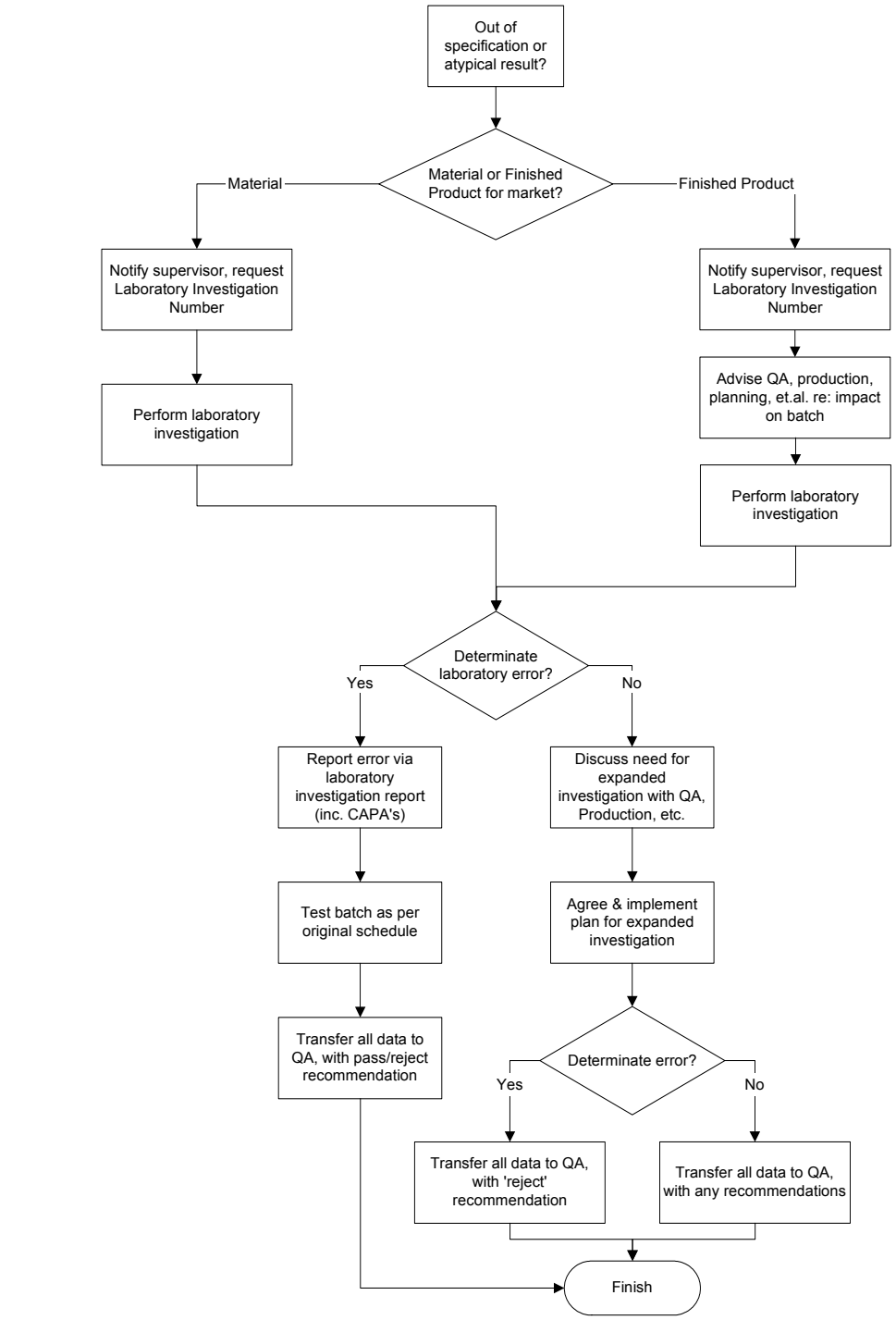


Diagram 8
Microbiological testing - Flowchart



Definitions
QA = Quality Assurance
CAPA = Corrective Action / Preventative Action

For further definitions, see QMS Glossary

Diagram 9
Microbiological Environmental Monitoring - Flowchart

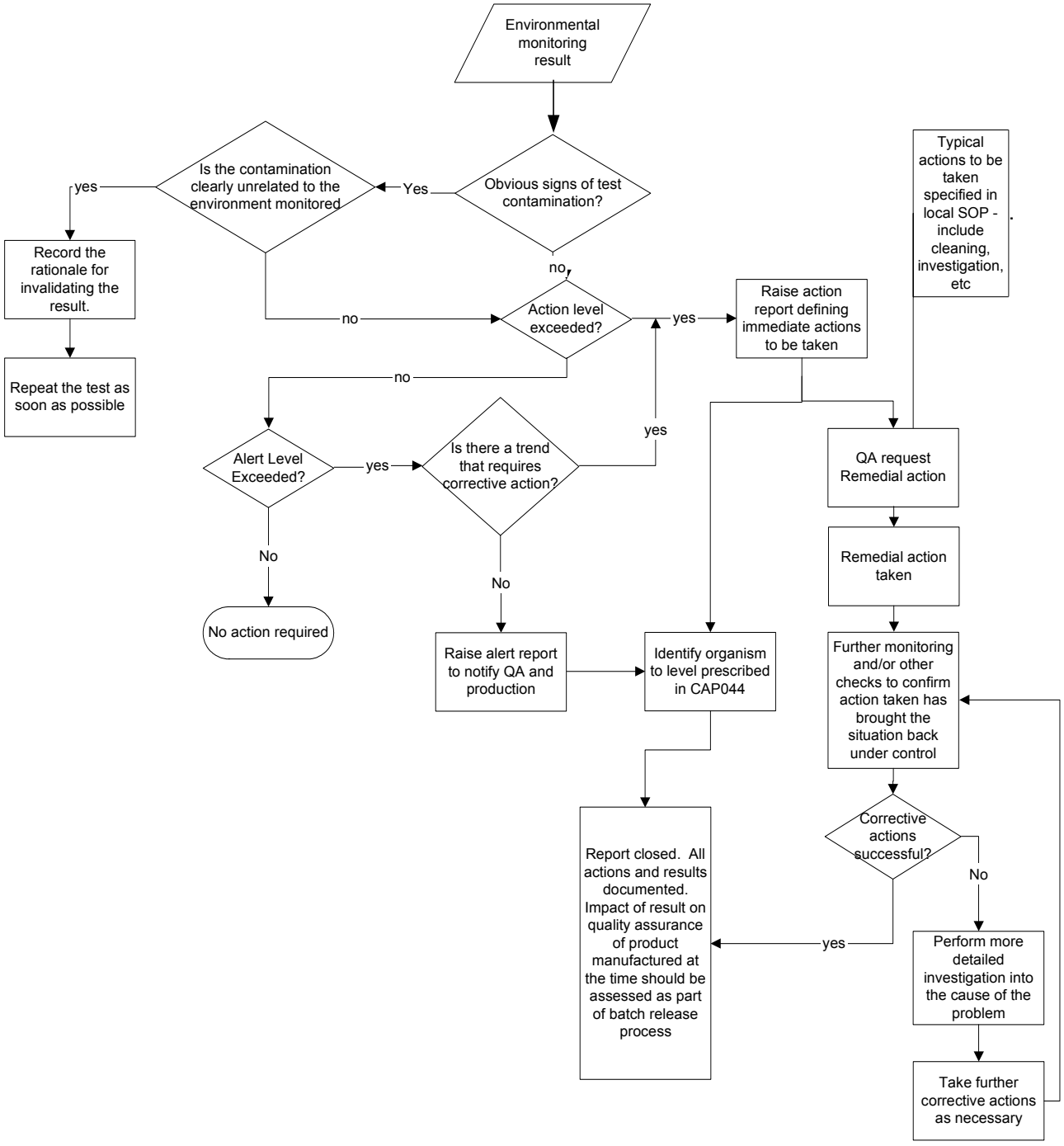
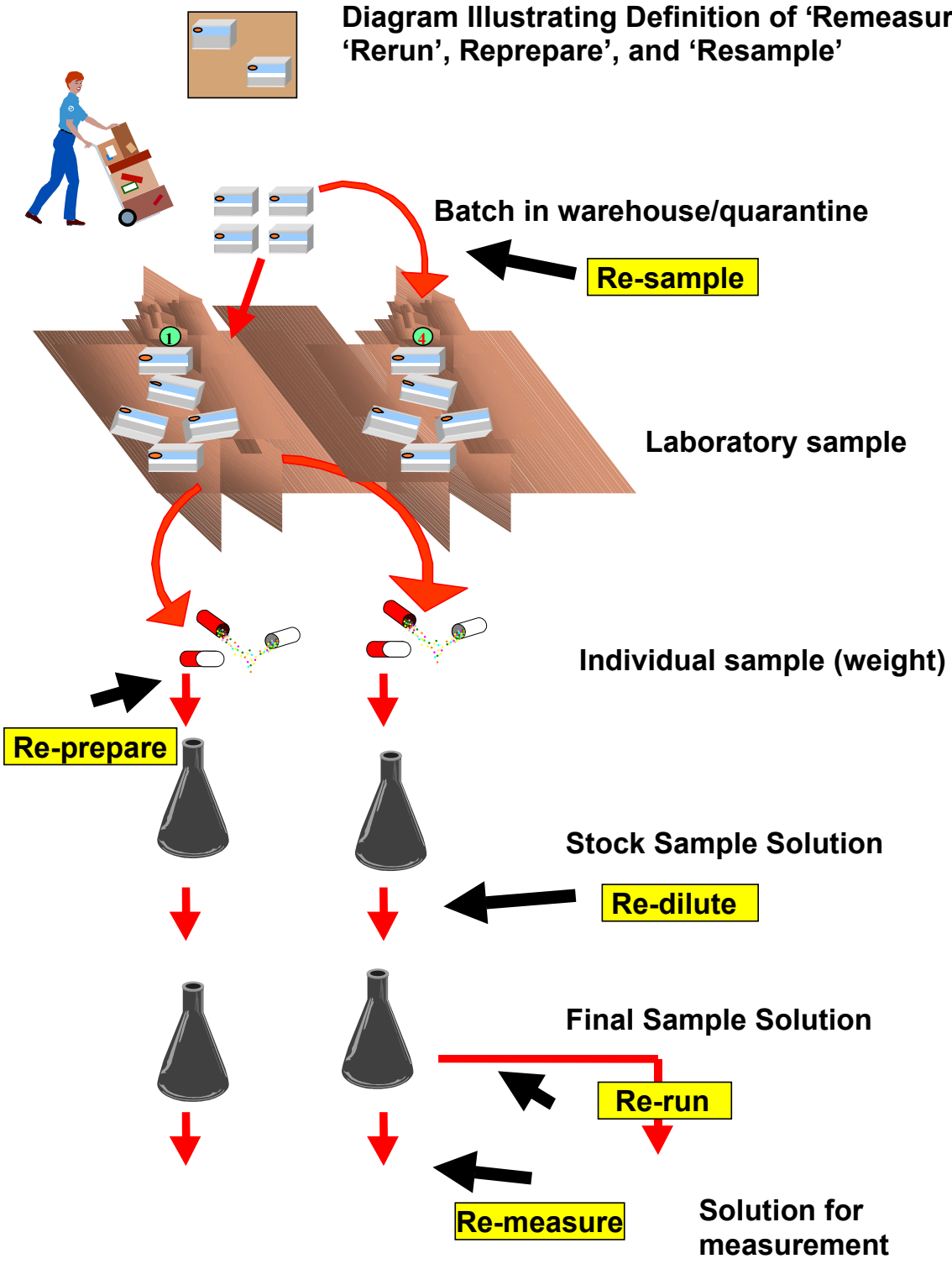


Diagram 10
Pictorial Representation of Common Terms



REFERENCES

GQG 6007	Deviation and Investigation Handling