1 Purpose

The purpose of this Guideline is to provide guidance for the investigation and response to Out of Specification (OOS) laboratory test results.

2 Scope and Applicability

This Guideline applies whenever a laboratory test result is out of specification. It may apply to any laboratory, its joint ventures and licensees who operate to cGMP standards. Contract laboratories, performing GMP work, would be expected to follow equivalent procedures which should be confirmed as part of the contractor selection process.

It is applicable to excipient, component, raw material, intermediate, active pharmaceutical ingredient and finished product release testing, stability testing and any other testing where the material has regulatory, compendial or internal specification limits associated with it. It applies to chemical and physical tests.

The guideline does not apply to stressed stability testing which is normally conducted in the development phase within R&D, where OOS results may be anticipated and accepted. However, it is recommended that for all time points during a stability program where OOS results are initially reported, they are documented as an OOS although the investigation as described in this guideline may not be applicable. Further guidance is given in the body of this document.

It does not apply to biological tests where procedures for retesting are described in the relevant pharmacopoeias nor to in-process tests, which are used to trigger real time process/system adjustments during manufacture to prevent process drift.

For certain tests, including content uniformity, weight uniformity and dissolution, specific retesting procedures should be applied as defined in relevant pharmacopoeias. However, it is recommended that any initial OOS result is documented as described in this guideline and an initial laboratory assessment conducted.

Specific guidance for tests on multi dose inhalation products is also provided Some of the principles, including the recording, assessment, reporting and trending, described in the guideline may be applicable to Out of Trend (OOT) results.

3 Definitions

3.1 Out of Specification (OOS) Test Result

A laboratory test that is outside its regulatory or compendial limits. In some cases, there may be additional tests and/or limits that are used to assess the quality of a material, but are not included in registrations or compendia. In these cases, the general principles described here are useful, but more latitude is allowable in the disposition of the material as long as it meets its legal requirements.

accelerated stability testing.

4 Responsibilities

4.1 Department / Function

It is the responsibility of each department or function to put in place procedures for the handling of OOS and OOT test results.

4.2 Analyst

The analyst is responsible for:

- Being aware of potential problems that could occur during the testing and watching for problems that could create inaccurate results.
- Ensuring that all equipment used are suitable for their use and properly calibrated when appropriate.
- Ensuring that all system suitability requirements are met.
- Reporting an OOS or OOT result to Line Management.
- Investigating the result together with Line Management.

4.3 Line Management

Line Management is responsible for:

- Conducting the initial laboratory assessment and extended investigation, where appropriate.
- Preparing the report with the analyst.
- Determining the protocol for retesting where required.

4.4 Quality Assurance (QA)

QA is responsible for:

- Ensuring that the extended investigation is carried out, where required.
- Determining the disposition of batches subject to a confirmed OOS result, for batches intended for commercial distribution, clinical studies and for stability studies supporting MAA/NDA.
- Ensuring that trending of OOS and OOT results is carried out.

4.5 Project Team within R&D

The Project team within R&D is responsible for:

- Assessing the implications for an OOS test result obtained during stability studies, including those from accelerated and stressed studies, with respect to defining and supporting specifications and/or product shelf lives.

brought to the attention of management for appropriate action.

Where a process related error has occurred the OOS result may be accepted and the laboratory phase of the extended investigation, i.e. extensive retesting, may be unnecessary.

Certain analytical methods have system suitability and calibration requirements and analyses not meeting these requirements should not be used. Any data collected during the suspect time period should be identified and not be used.

System suitability failures as well as failure of standard injections during a run must be documented. A pattern of such failures requires investigation. In these cases, the investigations need not be documented using the ñOOS procedureò.

Additionally, if a specific analytical method and/or a standard operating procedure (SOP) for a given technique has defined acceptance criteria for replication of injections and the replication for the sample is outside these criteria, these data should not be used and re-analysis as per original test should be undertaken. These data must be documented and any pattern of poor replication investigated.

If errors are obvious such as spilling of a sample the analyst shall not continue with an analysis that would be invalidated at a later time for this assignable cause. In this instance an OOS investigation is not required provided the analyst immediately documents what happened in the analytical records.

If the OOS result is for a test such as dissolution or content uniformity, where individual dosage units are assessed, a retest at the same stage is only appropriate if an identifiable cause was found during the initial assessment.

To be meaningful, the investigation must be thorough, timely, unbiased, well documented and scientifically defensible. The first phase of such an investigation should include an initial assessment of the accuracy of the laboratoryôs data, before test solutions are discarded, whenever possible.

A written record of the investigation must be made including the conclusion of the investigation and follow-up.

All OOS results shall be trended. This may be done by means of a log, which should be reviewed periodically in order to detect developing trends. Quality Assurance should ensure that trending is carried out but it may be undertaken by the laboratory function. The frequency of trending may depend on the frequency of OOS results; for R&D where analyses may be less frequent than in Operationsô laboratories, an annual trend is considered adequate. For Operations, where large throughput of analyses may be undertaken, a quarterly trend may be more appropriate.

It is recommended that some of the principles described here are applicable to observed OOT results. For example, OOT results should be documented and there should be an initial laboratory assessment to see if there is evidence of a laboratory error. Retesting may be appropriate if a confirmed laboratory error is found otherwise the result is accepted. The assessment and implications should be

clearly demonstrable, not just a supposition. The re-analysis is equal in number to that used for the normal test and the re-analysis results replace the original results. In addition, the investigation should extend to other samples, which may have been tested using the same equipment or by the same analyst and actions should be taken to prevent recurrence of the laboratory error.

Laboratory errors should be relatively rare. Frequent errors suggest there may be a problem that might be due to inadequate training of analysts, poorly maintained improperly calibrated equipment or careless work. These frequent errors must be investigated to determine the source of the error and correct and preventative actions implemented.

5.2.2 Laboratory or Sampling Error Not Confirmed

When the initial laboratory assessment does not determine that a laboratory or sampling error caused the initial OOS result, two possibilities remain - that the result reflects the actual batch condition or that the result is due to an unidentified laboratory error. Both possibilities must be investigated using an extended investigation in accordance with predefined procedures.

5.3 Extended Investigation

This investigation may comprise of two phases, a laboratory phase and a product/manufacture phase and may be conducted sequentially. Either phase may be commenced first. (Usually for Operations the laboratory phase of the investigation will be conducted first.)

The OOS investigation, including both laboratory and product/manufacture phases, if required, must be completed in 30 working days of the initial checked result. Any extension beyond this timeframe should be rare and must be justified and documented.

For example, for R&D during the manufacture of an active pharmaceutical ingredient (API), and where an OOS result is obtained on a batch of raw material or intermediate, it may be appropriate to conduct the product/manufacturing phase of the investigation prior to any retesting. If this investigation confirms that the OOS result is process related, the result may be accepted without the need for retesting. The batch may be rejected, reworked/reprocessed or subjected to user trial processing without retesting. The user trials may be undertaken to confirm that the OOS result does not have an adverse effect on the processing and/or quality of the next stage of manufacture. In these cases an OOS result during development can be accepted and used to justify changes in the specification for the raw material and intermediate. If OOS result is accepted the batch may be rejected and subjected to reprocessing or reworking. Where the investigation is inconclusive, extensive retesting should be carried out as part of the laboratory phase of the extended investigation.

5.3.1 Laboratory Phase of the Extended Investigation

Where the initial laboratory assessment has not found a laboratory error or the

products e.g. Metered Dose Inhaler products (MDIs) and Dry Powder Inhaler products (DPIs).

An OOS result obtained during a delivered dose uniformity test or particle size distribution test, where specific dose regimens are defined, shall only be discarded if there is unequivocal evidence that a laboratory error has occurred in the analysis.

Typically for such tests, numerous containers from the batch (or stability Time point) are taken and samples from individual containers taken, representing the delivered dose throughout the container life (e.g. beginning, middle and end) may be analyzed. This may provide a large data set of individual results for the initial analysis.

Where appropriate, retesting on the same container (which had the OOS) may be done to facilitate the investigation, it is recommended that a minimum of 2 full analyses be carried out where an individual OOS result is obtained to gather additional data for reporting and/or batch disposition assessment purposes.

All results must be reported for regulatory submission and batch disposition purposes. The results of retesting, along with the retesting protocol and any conclusions, shall be documented in a report/completed worksheet and reviewed prior to batch disposition. For other parameters, e.g. assay and moisture, a number of determinations from a specified number of individual containers may be defined in the method and the result for the batch may be the mean of all determinations. Where an OOS result is obtained from one of the containers an extensive retest from the same container is allowed, where this is sufficient product. This testing, plus any additional testing of new containers, may be used provide additional data for consequent use in assessing the final disposition of the batch.

If all determinations meet the requirements and although all results must be considered for batch disposition decisions and following an extensive investigation, it may be concluded that the initial OOS result did not reflect the true quality of the batch and that the batch may be considered suitable for release. Where the repeat determinations from the same container indicates a further OOS result(s), a minimum of 5 full analyses as defined in the method are recommended and a product/manufacture phase of the extended investigation conducted as described below in 5.3.2 is required. All results must be considered in batch disposition decisions.

5.3.1.2 Outlier Tests

Outlier tests should generally be used in the context of an extended investigation, may be used infrequently and based on scientific judgment

Outlier tests shall not be used for tests such as content uniformity or dissolution where the variability of individual units within the batch is being assessed.

The use of outlier tests for validated chemical tests with a small variance where

- The average should not include any initial OOS results.
- The average should include the satisfactory initial results and satisfactory retest results.
- Consider the following examples:

1. The initial analysis was a duplicate weighing and one result was OOS, triggering the investigation according to this guideline. There was no evidence of laboratory error, manufacturing or processing error and a further five sample weighing were taken, and shown to be satisfactory. The reportable result for purpose of the Certificate of Analysis or LIMS reportable result is considered to be the mean of the initial satisfactory result and the five retest results.

2. The initial analysis was a duplicate weighing and one result was OOS. Where the investigation, according to this procedure, concluded that a laboratory error had occurred, resulting in a normal retest (duplicate weighings), the reportable result would be mean of the duplicate retest results.

5.3.1.4 Re-sampling

Under normal circumstances data obtained from re-sampling cannot be used to release product unless it has been shown that there was a sampling error or that the sample was stored improperly and/or that the original sample was not representative of the batch.

Where a sampling error has been found, an assessment should be made as to the implications of the error on other batches sampled in the same manner.

Re-sampling is also permissible where there is insufficient quantity of the original sample to undertake the extensive retesting.

Re-sampling should be performed by the same qualified 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 shall be developed, qualified and documented.

5.3.2 Product/Manufacture Phase of the Extended Investigation

When the laboratory phase of the investigations 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 shall be conducted.

The objective of such an investigation shall be to identify the source of the OOS result. Varying test results could indicate problems in the manufacturing process, or result from sampling problems.

The product/manufacture phase of the investigation shall involve QA and personnel from other departments as required. The purpose of the formal investigation is to determine whether a process error has occurred.

does not meet its established standards and should result in batch rejection. For instances where there is an inconclusive investigation, those in which the cause of the OOS is not determined and the OOS result cannot be confirmed, the OOS results and all other results should be given full consideration in the batch disposition decision. This assessment should be fully documented.

5.5 Cautions

Where a series of assay results (to produce a single reportable result) are required by the test procedure and some of the individual results are OOS, some are within the specification and all are within the known variability of the method, the passing results are no more likely to represent the true result than the OOS results. For this reason, it is recommended that the reportable average is treated a OOS and investigation undertaken. Similarly, an assay result which is low but within specification and which may be supported by other tests, e.g. dissolution and/or content uniformity should be cause for concern, and caution exercised in release or reject decisions.

5.6 Stability Testing

5.6.1 Reporting of OOS Results in Development Stability Programs

An OOS result in development stability programs, including up to MAA/NDA may provide data to support the establishment of specifications and/or product shelf lives or in some cases, changes to previously agreed specifications/shelf lives.

These results may be obtained from long term, accelerated or stressed conditions. In all cases, the OOS should be documented as described in this guideline. For the first occurrence of an OOS in a given stability program, an investigation as described shall be undertaken. If the result is accepted and considered to be a true measure of the batch, investigations of OOS results for the same test at subsequent time points may be less extensive but documented in the laboratory work sheets/notebook, referencing the initial OOS investigation and results accepted.

The project team within R&D shall assess the implications of the OOS test result obtained, with respect to specifications and/or product shelf lives and define the strategy for continuing the stability program when OOS results have been obtained.

