STANDARD OPERATING PROCEDURE

Laboratory Data Management;

Out of Specification (OOS) Results

Name and Role	Date
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Document Revision History

Version	Date	Reason for Change	Status
V 1.0	11-Oct-2011	First approved version of this SOP. Used as input for public review at ECA OOS Forum Prague June 2012	Released
V 2.01	11-Jul-2012	Draft version 2 by CB & BR based on inputs from OOS Forum and informal comments by FDA	Draft
V 2.01	11-Jul-2012	New appendix III added	Draft
V 2.02	01-Aug-2012	Technical Approval & Release process	Draft
V2.0	10-Aug-2012	Second approved version	Released
V2.1	09-Aug -2013	Typo graphical errors in Appendix 2 corrected	Released

Scope & Application

This procedure applies to physicochemical -based laboratory testing. 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. It is not applicable to PAT (Process Analytical Technology) or RTR (Real Time Release) approaches.

In addition, it is intended to cover only continuous variables, for example assay, impurity values, hardness etc., which may be assumed to be normally distributed. It is not intended to cover discrete variables, for example, particle counts, identity tests or cosmetic quality defects derived from AQLs. This procedure is confined to the analytical laboratory and does not apply to microbiological testing.

Specifically;

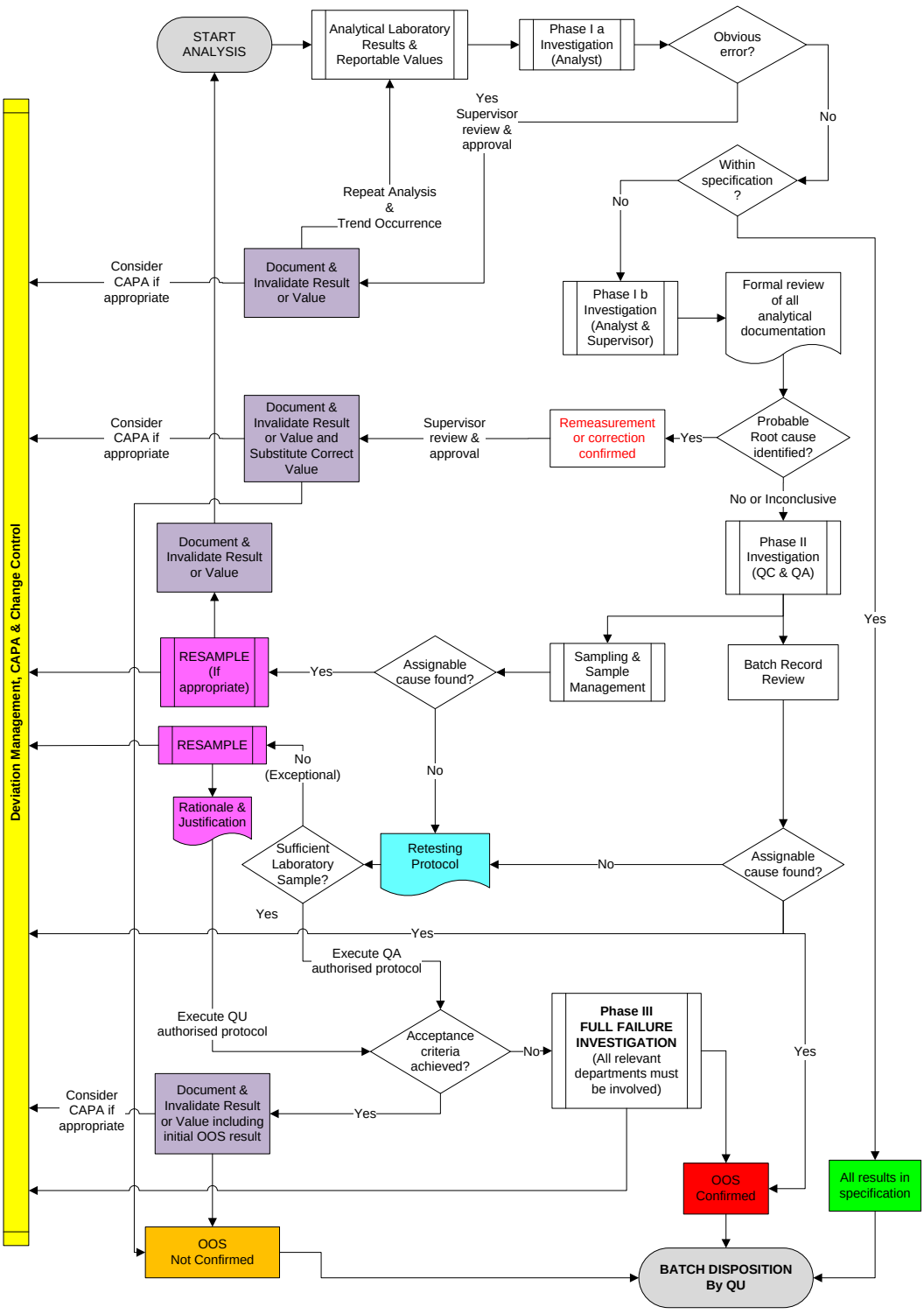
- Batch release testing and testing of starting materials.
- Registered In-Process Control testing if data are used as part of for batch evaluation or certification
- Stability studies on marketed products and or active pharmaceutical ingredients (ongoing and follow up stability)
- Batches for clinical trials or IMPs.

If at the end of Phase II of the OOS investigation, no assignable root cause has been identified, a full failure investigation will be undertaken. This should be conducted under other procedures and is not covered by this SOP.

Regulatory References

1. Guidance for Industry; Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production, US Food and Drug Administration, FDA, (CDER), October 2006
2. Out Of Specification Investigations, Medicines and Healthcare products Regulatory Agency, UK, (MHRA) November 2010 http://www.mhra.gov.uk/Howweregulate/Medicines/Inspectionandstandards/GoodManufacturingPractice/FAQ/OOSFAQs/index.htm
3. Evaluation and Reporting of Results, OMCL Network of the Council of Europe, Quality Assurance Document. PA/PH/OMCL (07) 28 DEF CORR, December 2007
4. USP 35 (2012) General Chapter <1010>, ANALYTICAL DATA; INTERPRETATION & TREATMENT
5. ISO 5725-5 (1989) Accuracy (trueness and precision) of measurement methods and results —Part 5: Alternative methods for the determination of the precision of a standard measurement method; Section 6.2 Robust analysis Algorithm A page 35

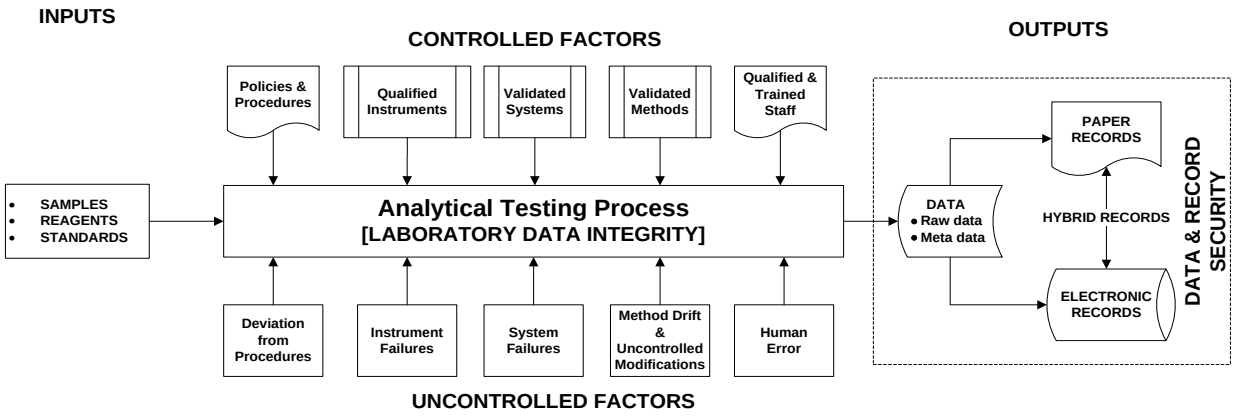
6. SOP Process Flow



Overview of Laboratory Data Management & the Analytical Process

Laboratory data quality management processes are a part of the overall Quality Management System as required by Chapter 1 of EU GMP and the FDA cGMPs as specified in 21 CFR §210 & §211.

Analytical processes and procedures are managed as part of a lifecycle concept. Laboratory data integrity and security are critical requirements under the GMPs. Such a process is illustrated below.



The purpose of this SOP is to define the procedures for managing laboratory data which are out of specification. Managing laboratory data which are Out-of-Expectation (OOE) or Out -of-Trend(OOT) are subject of a separate SOP.

QU involvement

The flow chart is a high level process guide to the SOP and is not intended to include all details or eventualities in this SOP. Quality Control testing is considered an integral part of the Company's Quality Unit as explicitly required by EU GMP. Formal Quality involvement, eg by a separate QA function, is kept to the minimum consistent with US & EU regulatory expectations and requirements based upon published legislation and guidelines as well as the Core Team's experience. The extent of Quality oversight is very dependent on individual company requirements.

Organisation and nomenclature of Quality Control and Assurance functions and assignment of responsibilities are also highly company specific. This SOP does not dictate or recommend specific steps that must be supervised by specific quality functions other than those required by regulation. Therefore the term Quality Unit (QU) as used in the revised chapter 1 of EU GMP Guide, is used here.

The initial investigation, however, should be performed directly under the responsibility of the competent laboratory.

Reportable values (results)

As defined in the Technical Glossary (Appendix 4), a reportable value or result is the predefined combination of analytical measurements to arrive at a final analytical result which is compared with a registered specification.

An analytical method/procedure might consist of a specific number of replicates to arrive at a reportable value or result.

Performing more than one measurement (replicate measurements) is a valid and acceptable approach to reduce analytical variability of the reportable result derived from these replicate measurements. This predefined combination of analytical measurements must be formally written in the analytical method/procedure used.

In this instance, individual analytical measurements are NOT compared with the registered specification. However, they all must lie within the known predefined acceptance criteria based on the analytical method/procedure's process capability which are also documented in the analytical method/procedure.

The reportable value or result is derived from one full execution of that method/procedure, starting from the original (homogeneous) laboratory sample.

For instance;

1. an HPLC assay 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 reportable result. The spread of the individual peak responses would need to meet the acceptance criteria set in the analytical method/procedure before the averaging took place.

2. In some cases, eg assays, a series of sample preparations from the same homogeneous laboratory sample constitute the method/procedure. It is appropriate to specify in the method/procedure that the average of these multiple sample preparations from the same homogeneous laboratory sample is considered to be one test and represents one reportable result.

   Limits on acceptable variability among the individual assay results is based on the known variability of the validated method/procedure and specified in the authorised written method/procedure.

   If the individual assay results do not comply with these limits, the test is invalidated.

   Note that the individual values from a series of sample preparations from the same homogeneous laboratory sample are NOT compared with the registered specification.

Gross Laboratory Errors & System Suitability Failures (Phase Ia)

The Phase la investigation is to determine and document if there has been a clear obvious laboratory error or the basic data quality fails system suitability acceptance criteria. This is the responsibility of the Analyst to perform and the Supervisor to confirm. If a clear obvious laboratory error occurs the procedure must be stopped and the Supervisor informed immediately.

Examples of a clear obvious laboratory error are;

- Spillage of sample or standard materials
- Incorrect volumetric glassware used
- Instrument or system malfunction
- Incorrectly set instrument or system parameters
- Wrong standard or reagents used
- Sample preparation problems

If this is a recurrent problem raising a CAPA will be appropriate.

The number and type of clear obvious laboratory errors should be trended as part of the overall Laboratory Data Management system.

The Analyst must ensure that only those instruments meeting established performance specifications are used and that all instruments are properly calibrated. The Analyst is responsible for checking that analytical measurement data are within the predetermined acceptance criteria for System Suitability as defined in the analytical procedure. All sample and standard preparations must be retained and only disposed of after the Supervisor has signed off any investigation.

Examples of System Suitability failures are;

- System precision exceeded at the start or the end of a chromatographic run
- Permitted range of analytical measurements or results exceeded
- Standard responses drifting beyond predetermined limits
- Non conformance of chromatographic parameters as defined in USP <621> and Pharm. Eur. 2.2.46

System Suitability failures 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.

The supervisor will determine the appropriate remedial actions to be taken. A CAPA would normally be expected to be raised in the case of System Suitability failures if the root cause is not trivial.

The documentation of this investigation is conveniently handled using a simple check list. An example of a generic model check list is given in Appendix 1.

If gross analytical errors or system failures are identified, the data are invalidated and documented in the analytical record. The analysis is repeated using the original laboratory sample in accordance with the analytical procedure.

If no gross analytical errors or system failures are identified, proceed to Phase 1b.

Laboratory Data Record Errors (Phase Ib)

In the absence of a clear obvious laboratory error or system suitability failure a Phase lb investigation is carried out to review the analytical process and record to determine if a laboratory root cause can be assigned. This is the responsibility of the competent Supervisor and should cover at least;

- Establishing that the correct sample(s) were tested.
- Confirming that sample integrity was maintained in the laboratory.
- Reviewing that all instrumentation and systems used in the testing were within calibration date and log books reviewed for any changes.
- Confirming that the Analyst was trained to carry out the method.
- Discussing the test method with the Analyst and confirming analyst knowledge of and performance of the correct procedure.
- Examining the actual samples and standards used and any of the solutions prepared.
- Examining the raw data obtained in the analysis, including chromatograms and spectra, and identifying any anomalous or suspect information or appearance.
- Reviewing environmental temperature/humidity data within the area whilst the test was conducted.
- Determining that appropriate reference standards, solvents, reagents, and other solutions were used.
- Identifying any previous issues with this procedure.
- Identifying other potentially interfering testing/activities that occurred at the time of the testing.
- Verifying that the calculations used to convert raw data values into a result(s) and reportable value are scientifically sound, appropriate, and correct.
- Fully documenting and preserving records of this Phase of the laboratory assessment.

As a result of this investigation, there may be a laboratory error hypothesis concerning the root cause of an OOS result. This may be confirmed by reappraisal and/or remeasurement of the previously prepared solutions. Retesting is not appropriate at this stage.

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, insufficiently detailed written methods/procedure or careless work.

Whenever a laboratory error is identified, the source of that error should be determined, corrective action and, if appropriate, preventative actions taken.

If a laboratory error is identified, the initial OOS data are invalidated and recorded in the analytical documentation. The analysis should be repeated using the original laboratory sample in accordance with the original analytical procedure.

If the Phase 1b investigation is inconclusive and does not identify a root cause for the OOS result, a full Phase II laboratory failure investigation is undertaken under the control of the Quality Unit.

Full Laboratory Investigations (Phase II)

Before consideration of any retesting, the Quality Unit must conduct a review of batch records to ascertain if any deviations or errors in the production or sampling process might indicate the root cause for the OOS result in accordance with an established procedure not covered by this SOP.

If the outcome of this QU review is negative, a protocol for the retesting of the original laboratory sample with the intention of 'isolating' or confirming the OOS result should be prepared. under the control of the QU.

Very infrequently, resampling may have to be carried out. In this instance, a documented rationale for and justification of this activity must be carried out.

Outlier testing

On rare occasions, a reportable 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.

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 in accordance with an SOP.

An outlier test is of value in estimating the probability that the OOS result is discordant from a data set. This information can be used in an auxiliary fashion, along with all other data from an investigation, to evaluate the significance of the result. However, a statistical outlier test will not identify the cause of an extreme observation and, therefore must not be used to invalidate a suspect result alone.

Outlier testing must be used with extreme caution. The use of any outlier test and the minimum number of results required to obtain a statistically significant assessment from the specified outlier test must be approved in advance by the QU.

A description of some possible test approaches is given in Regulatory Reference 4. A robust method is to be preferred as non robust tests are strongly influenced by the nature of the outlier itself.

Retesting protocol

The retesting protocol will be authorised by the Quality Unit and contain at least the following sections;

1. The purpose of the retesting
2. The method to be used. The number of retests relate to the number of complete executions of this method including standards.
3. The use of a second analyst if considered appropriate
4. The maximum number of retests to be performed on the sample should be specified in advance. This can be based on scientifically sound statistical principles as described in USP General Chapter <1010>. In addition, the procedures of Hofer[1] or Andersen[2] may be usefully consulted.
5. Methods of data evaluation are defined.
6. The acceptance criteria for the successful isolation of the OOS result must be defined. This will include that all retest results are within specification and the spread within the known process capability of the method.
7. The 95% confidence intervals of the data including the initial OOS result must also lie within specification. A description and examples of a simple approach are given in Appendix 2.
8. Preferably a 95% confidence interval using a robust method of estimating the mean and standard deviation can be undertaken such as described in ISO 5725-5 (1989) [Regulatory Reference 5] or its extension to Huber's H15 method. This approach is briefy described in Appendix 3. These approaches are more mathematically demanding but are more statistically sound.
9. An evaluation of all data and a conclusion of the outcome of the retesting.

The chosen retesting rationale must be scientifically sound and well documented. It is proposed by the Company and should be defendable to the Competent Authority. The approaches outlined in Appendices 2 and 3 are only examples of suitable approaches. Other equally valid approaches may be adopted.

If all the acceptance criteria in the approved retesting protocol are met the batch is considered to be within specification. However the initial OOS result cannot be invalidated as no assignable root cause has been established. All data must be documented in the analytical record. The value for the analytical value is taken as the mean of the retest data without the original OOS result.

If the Phase II investigation fails to isolate the OOS result or is inconclusive as it does not identify a root cause for the OOS, a full Phase 3 investigation is undertaken under the control of the Quality Unit.

A full Phase III investigation is not the subject of this SOP.

[1] J D Hofer, Considerations When Determining a Routine Sample Size for a Retest Procedure, Pharmaceutical Technology NOVEMBER 2003

[2] S Andersen, An alternative to the ESD approach for determining sample size and test for Out-of Specification situations, Pharmaceutical Technology MAY 2004

Appendix 1; Checklist for Phase 1a OOS investigation

Sample/Laboratory Reference:	
Analytical Method Number:	
Date & Time of the Investigation:	

OBVIOUS OR GROSS ERRORS

☐ Weighing error	☐ Instrument or equipment malfunction
☐ Sample or standard spillage	☐ Instrument parameters incorrectly set
☐ Incorrect pipette used	☐ Incorrect Instrument used
☐ Incorrect volumetric flask used	☐ Power failure during analysis
☐ Volumetric dilution error	☐ External interferences; eg vibration, excessive airflows
☐ Contamination or cross contamination	☐ Sample management compromised
☐ Incorrect sample used	☐ Laboratory Sample storage compromised

Documented evidence

METHOD OR PROCEDURE DEVIATIONS

☐ Incorrect method/ procedure used	☐ Wrong Reference standard(s) used
☐ Instrument/System not calibrated	☐ Wrong Reference standard(s) preparation
☐ Wrong concentration range used	☐ Improper sample/standard solution storage
☐ Wrong grade of reagents/solvents used	☐ Analyst not trained to carry out method/procedure
☐ Environmental conditions not met	☐ Deviation for documented method/procedure requirements
☐ Improper sample/standard solution storage	☐ Method/procedure not followed
☐ Additional or missing peaks observed in a chromatogram	☐ Additional or missing peaks observed in a spectrum

Documented evidence

SYSTEM SUITABILITY FAILURES

☐ RSD of standards exceeded	☐ Range between injections exceeded
☐ RSD of samples exceeded	☐ Range between sample replicates exceeded
☐ Measurement outside validated range	☐ System suitability tests missing
☐ USP <621> or EP 2.2.46 criteria exceed	☐

Documented evidence

CALCULATION ERRORS

☐ Data transcription error	☐ Calculation formula incorrect
☐ Arithmetical error	☐ Incorrect factor used
Documented evidence	
Analyst (Date & Time)	
Supervisor (Date & Time)	

Appendix 2; Example calculation of a 95% Confidence Limit

Assume that the registered specification is 95.0 to 105.0% of claim and that an OOS result is obtained of 94.7.
The Phase II investigation fails to identify a root cause. QU authorise a retesting protocol for n=6 and the retest results obtained are; 98.0, 97.0, 96.1, 96.5, 97.4, 96.2.

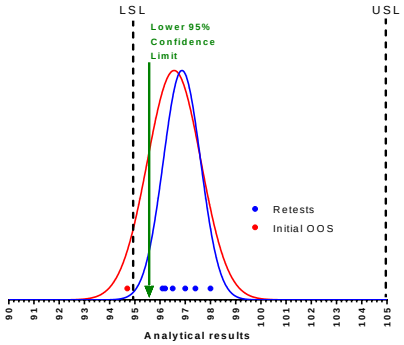
The lower 95% Confidence Limit is calculated for all n (7) results from the formula;

$$\bar{X} - \frac{t_{(0.05,n-1)}s}{\sqrt{n}}$$

where $\bar{X}$ is the mean of all 7 values, $t_{(0.05,n-1)}$ is the value of the t distribution for 6 degrees of freedom and s is the calculated sample standard deviation.

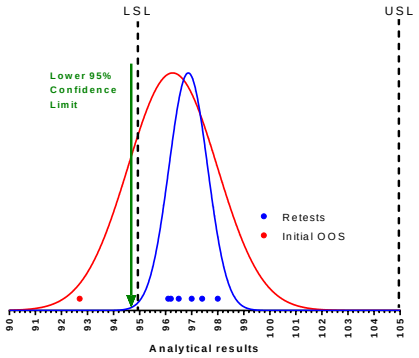
$$\bar{X} - \frac{t_{(0.05,n-1)}s}{\sqrt{n}} = 96.56 - \frac{2.45(1.06)}{\sqrt{7}} = 95.6$$

As this value is greater than the LSL of 95%, the 'isolation' of the initial OOS result is achieved.
The reportable value is hence the mean value of six retest results 96.9. This situation is shown graphically below.



However, if initial OOS result obtained was 92.7 instead of 94.7, the lower 95% confidence limit would have been 94.7 which is below the registered specification limit.

$$\bar{X} - \frac{t_{(0.05,n-1)}s}{\sqrt{n}} = 96.27 - \frac{2.45(1.71)}{\sqrt{7}} = 94.7$$



In this case, the 'isolation' of the outlier was unsuccessful.

Appendix 3; Example calculation of a robust mean and robust 95% Confidence Limit (H15 method)

In Appendix 2, the reportable value was calculated excluding the outlier which had been 'isolated' using a standard 95% confidence interval.

A more statistically sound approach is include this value using a robust procedure based on the median and deviations from it because medians are less influenced by outlying values. The method briefly described here is based on Huber's H15 method. This is more difficult to calculate than the standard confidence interval as it relies on an iterative procedure. However this is easily accomplished using an Excel spreadsheet without the necessity for macros. The mathematical details are given by Ellison, Barwick and Duguid Farrant[3].

However H15 has a major advantage in that the calculation includes the outlier as part of the data set and provides values for the robust mean and robust standard.

Briefly, the algorithm used is as follows;

1. Calculate the initial estimates of the median and robust standard deviation

$$x_0^* = \text{Median}[x_1 .... x_n]$$
$$s_0^* = 1.483 \text{Median} \left| x_i - x_0^* \right|$$

2. Evaluate all the data points using

$$x_i^* = \begin{cases} x_{i-1}^* - 1.5 s_{i-1}^* \text{ if } x_i^* < x_{i-1}^* - 1.5 s_{i-1}^* \\ x_{i-1}^* + 1.5 s_{i-1}^* \text{ if } x_i^* > x_{i-1}^* + 1.5 s_{i-1}^* \\ \text{otherwise} \\ x_{i-1}^* \end{cases}$$

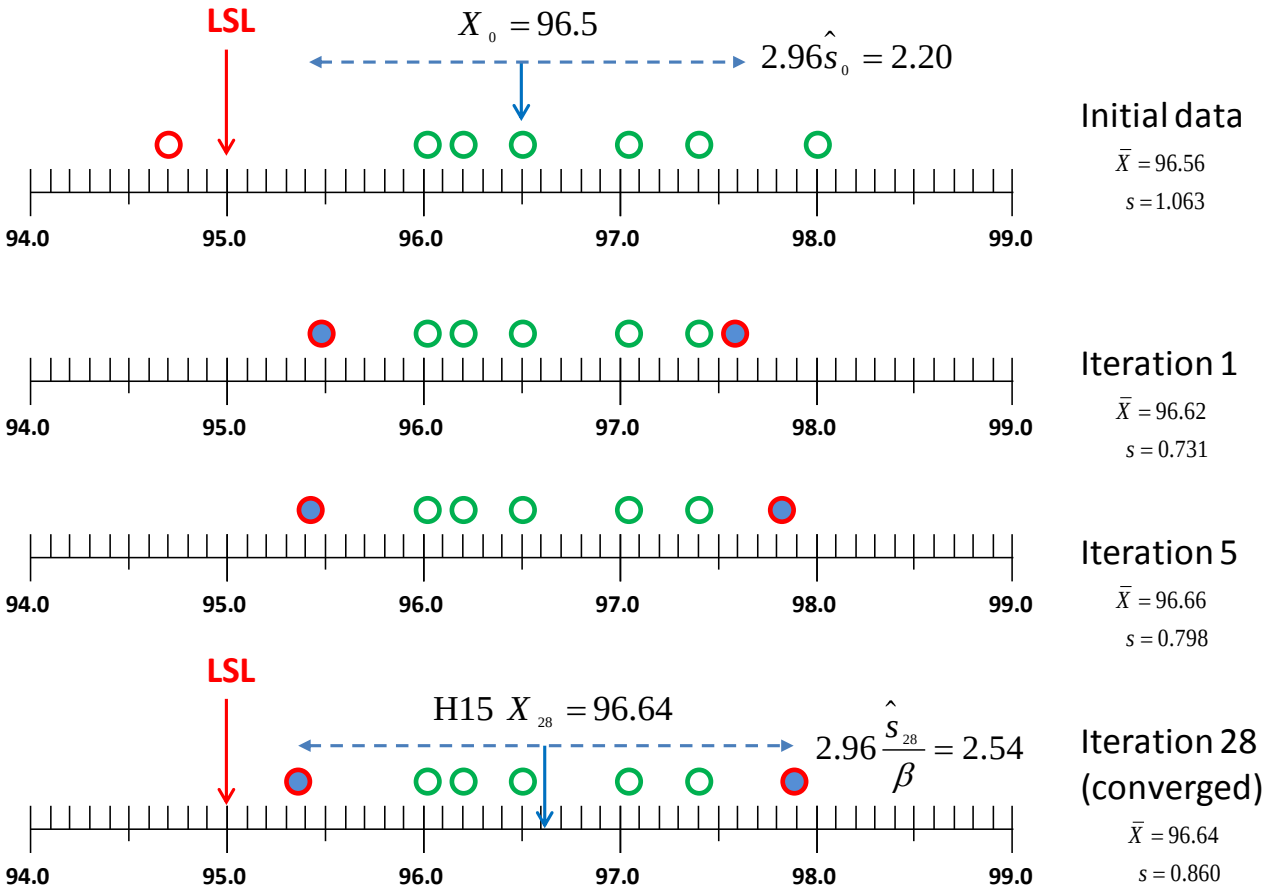
   This replaces points outside the range with values at the calculated 99% confidence limits but leaves other values unchanged

3. Update the estimate for the standard deviation based on the current estimate with a correction factor, β, for the normal distribution.
4. Repeat steps 2 and 3 for the updated data until the values for the robust mean and robust standard deviation no longer change, for example , by 0.1%

It is easier to understand the process graphically using the same data set as Appendix 2

[3] Ellison SLR, Barwick VJ, Duguid Farrant TJ, ***Practical statistics for the Analytical Scientist***, Section 5.3.2; Robust estimators for population means, Royal Society of Chemistry, 2009, ISBN 978-0-85404-131-2

The initial OOS result is shown in red and the retest data are shown in green data in the figure below under initial data. The lower specification limit (LSL) is also marked on the dot plot. The initial iteration moves both the initial OOS result and one retest result to the calculated confidence interval. Note that 65 of the 6 retest results are unchanged throughout the calculation. As the iterations proceed the robust mean and robust standard deviation changes until the values converge. After 28 iterations, convergence is obtained and the 99% confidence interval is well within the specification and the robust mean value for the reportable value based on all 7 data points of 96.64 is determined. For comparison, the values of the mean and standard deviation are given for the initial data and for each iteration.



Appendix 4; Technical Glossary

Acceptance Criteria	Numerical limits, ranges, or other suitable measures for acceptance of the measurements or results of analytical methods and procedures
Analytical Measurement	The output from an instrument or procedure eg absorbance or peak area.
Analytical Result	The conversion of an analytical measurement to a property of the sample eg concentration.
CAPA	Corrective Action and Preventative Action system to manage significant deviations.
Change Control	A formal system to manage planned events or differences from policies, procedures or standards.
Confidence Interval	A range of values so defined that there is a specified probability (normally 95%) that the value of a measurement or result lies within it.
Deviation	An unplanned event or a difference from procedures or standards.
Gross Error	A mistake or systematic error that would cause a measurement to be invalid or biased.
Original Laboratory Sample	The representative sample obtained from the batch by a scientifically sound sampling procedure.
Out of expectation result (OOE)	An atypical, aberrant or anomalous result within a series of results obtained over a short period of time but is still within the acceptable range specification.
Out of Specification result (OOS)	A result that falls outside established acceptance criteria which have been established in official compendia and/or by company documentation.
Out of Trend result (OOT)	A time dependent result which falls outside a prediction interval or fails a statistical process control criterion.
Outlier	A measurement or result which lies outside the expected distribution of sample measurements or results at a defined level of confidence.
Protocol	An approved document which specifies the extent of testing and methods for data evaluation.
Random Error	Errors in measurement that lead to measured values being inconsistent when repeated analytical measurements are made.
Remeasurement	The repeat of an analytical measurement on prepared solutions to test a postulated root cause hypothesis.
Reportable Value (Result)	The predefined combination of analytical measurements to arrive at a final analytical result which is compared with a specification.
Resampling	Any additional units collected as part of the original sampling procedure or from a new sample collected from the batch, should that be necessary.

Retesting	The repeat of an analytical procedure using the original sample under a protocol to isolate an initial OOS, OOE or OOT result for which no root cause could be identified.
Root Cause	An assignable cause identifying the reason for obtaining an OOS, OOE or OOT result.
Specification	A list of tests with references to analytical procedures and appropriate acceptance criteria.
Standard Error of the Mean	The error of a mean value (of n determinations) at a specified probability (normally 95%) determined by the product of the value of the estimated sample standard deviation and the value of the *t* distribution with n-1 degrees of freedom divided by the square root of the number of determinations, n.
System Suitability Test	A test to ensure that analytical data are within the predetermined acceptance criteria for an analytical system based upon the known analytical process measurement capability.