### 3.2 Accelerated Stability Testing

Studies designed to increase the rate of chemical degradation or physical change of a drug substance or drug product by using exaggerated storage conditions as part of formal stability studies.

### 3.3 In-Process Test

Test performed during production which may trigger real time equipment/system adjustments to prevent process drift and to ensure conformance with the required quality/specifications.

### 3.4 Laboratory Error

Incorrect performance of one or more of the steps of an analytical procedure and/or any identifiable laboratory related problem such as malfunctioning equipment etc.

### 3.5 Original Sample

The sample that was originally collected for the purpose of laboratory testing. This can be either the original test solution, a test preparation such as a tablet grind, or the group of tablets, capsules, vials or other dosage forms which were originally designated as laboratory samples.

### 3.6 Outlier Result

A result which is statistically different to the other results for a batch when assessed using a suitable statistical tool, e.g, Dixon's outlier test.

### 3.7 Out Of Trend (OOT) Test Result

A laboratory test that is within its regulatory or compendial limit but is atypical of previous results for the test over a number of batches or earlier time points in a stability study and may provide early indication of a potential OOS result. The importance of OOT results increases as the knowledge of the product increases and more latitude in interpretation of, and response to, an OOT result may be appropriate in early development compared to commercial product.

### 3.8 Process Related Error

An error caused by incorrect performance of the manufacturing steps, malfunctioning process equipment, or issues associated with changes of equipment, scale-up or other problems associated with the process.

### 3.9 Stressed Stability Testing

Studies designed to elucidate intrinsic stability of drug substance or assess the effect of severe conditions of the drug product. Such testing is normally part of the development activities and is carried out under more severe conditions than

 

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 documented. OOT results shall be trended and confirmed trends reported to QA. For commercial products this may be done via the Annual Product Review process.

## 5.2 Initial Laboratory Assessment

As soon as an analyst determines that a test result is OOS and before any further testing is carried out, the Line Manager must be notified. Together, they conduct a laboratory investigation to determine if a laboratory error can be identified as the cause of the OOS result. The Line Manager's assessment should be objective and timely. The following areas should be reviewed and documented, (the use of a pro-forma may be helpful):

- Test method and analyst's knowledge and ability to use it
- Check raw data, including chromatograms and spectra, and calculations, including changes to automatic calculation methods
- Performance and calibration of the instruments
- Review of quality of reference standards, reagents and solvents
- Method validation data, where applicable
- Check of sampling procedure

This phase of the laboratory investigation must include an intensive assessment of possible causes. The goal is to determine if a laboratory error occurred or if there is reason to suspect that an error occurred. A simple checklist approach is not sufficient and will only reveal a laboratory error in the most obvious circumstances. If this phase of the investigation is not comprehensive, valuable information concerning root cause may be lost.

The initial assessment can be greatly facilitated if all laboratory glassware, pipettes, reagents, and solutions are kept together until after the test results are calculated. It can be helpful during the course of the assessment to re-inject or otherwise re-read the original sample solution in order to identify instrument malfunctions or incorrect dilutions.

Each step of the assessment must be fully documented and the outcome reviewed prior to batch release or reporting of stability analyses.

The result from the initial laboratory assessment phase can be either of the two following:

- Laboratory or sampling error confirmed
- Laboratory or sampling error not confirmed

### 5.2.1 Laboratory or Sampling Error Confirmed

If the error is due to a written or calculation error, the error may be corrected without

 

personnel from other departments as required. The purpose of the formal investigation is to determine whether a process error has occurred.

The following general items should be included in the investigation as appropriate:

- The reason for the investigation.
- Responsibilities for actions including preparation of the final report.
- A review of the manufacture and a summary of the process steps that may have contributed to or caused the problem.
- The results of a review to determine if the problem has occurred previously
- Corrective actions required for the batch under investigation and its final disposition.
- Preventive actions required to prevent a recurrence of the problem.
- Other batches or products that may be implicated by the same employee(s), equipment, or process. Also, any corrective action that may be necessary for these batches.
- A review of the original laboratory assessment and/or reference to it.
- Results of any additional testing that may have been performed as part of the investigation.
- Signatures and comments of QA and other personnel who conducted and approved the investigation.

It may be appropriate to sample and/or retest specific parts of the batch to facilitate understanding as to which parts may be affected and which parts may not. The investigation must justify any considerations in treating parts of the batch differently than others.

If the investigation concludes that the OOS result was due to a process related error, then the OOS shall be considered valid and appropriate actions shall be taken.

Where a laboratory phase extended investigation had been conducted prior to the product/manufacture investigation, no further testing is acceptable. If the investigation is inconclusive, then an examination shall be made of all of the available data in the context of the product's history, in-process test results, and any other pertinent factors. Based on the above, a scientific judgment shall be made as to its disposition.

## 5.4 Concluding the Investigation

To conclude the investigation, the results shall be evaluated, the batch quality shall be determined, and a release decision shall be made.

Where the investigation concludes with part rejection/part release, this must be clearly justified and documented.

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.

In those instances where an investigation has revealed a cause and the suspected

 