1 Purpose

The purpose of this international guideline is to outline minimum mandatory requirements as well as recommendations for the identification and reaction to trends found in stability data.

2 Scope and Applicability

This guideline is applicable to all Commercial Stability Sites and contractors performing stability studies on commercial drug substances and drug products.

3 Definitions

3.1 Out of Specification (OOS) Result

A laboratory test result that is outside its regulatory or compendial limits.

3.2 Trend

A pattern of data that indicates change over time. This data may demonstrate either an increasing or decreasing trend (change of mean) for the stability indicating parameter over time or the data may indicate no discernible change at all. The change may be linear or non-linear.

3.3 Trending in Stability Studies

The evaluation of stability data (not necessarily statistical) in order to identify trends and their impact on the stability of a product.

3.3 Significant Trend

An average typical trend for a parameter that, in relation to release result variability and specification limits, may lead to an OOS result before or at end of shelf life for any batch released. The definition of the criterion for significant trend might differ between products, but could for example be defined as a certain proportion of the specification interval.

3.4 Out of Trend (OOT)

A single result or a number of results that do not follow the expected trend, for a particular batch or series of batches, either in comparison with other stability studies or with respect to previous results collected during a stability study. There are three types of OOT situations identified in this guideline: Atypical result, Atypical trend and Adverse trend.

3.5 Atypical Result

A single result that does not follow the expected trend for a stability indicating parameter compared to previous results from the same study.

Inform QP/senior QA Management at the site managing the contractor, if a significant trend has been observed

Report adverse trends according to QA Agreement

4.3 Lead Site

It is the responsibility of the Lead Team/Site (acting as the Commercial Stability Site) assigned to a contractor to ensure that the contractor has procedures in place to comply with this guideline. This responsibility shall be clearly documented in the relevant Quality Assurance Agreement.

4.4 QP/Senior QA Management

It is the responsibility of QP/senior QA Management at the formulation site, or site managing the contractor to:

Review the outcome of the trending reports issued by the Commercial Stability Site or contractor

Ensure that the product release specification is constructed in a way that provides a high probability that any batch released will remain within the registered specification throughout the retest period/shelf-life of the drug substance/drug product when stored according to the labeled storage conditions

React to reported adverse trends shown by a single batch or series of batches according to procedure.

5 Guideline

5.1 Introduction

The registered retest period/shelf life of a drug substance/product will have been set taking into account the specification to be registered and the trends seen in stability studies completed or ongoing at the time of new product and/or new primary pack registration. However, these studies will have been conducted on relatively few batches, some made only at pilot scale.

Therefore, the Commercial Stability Site must use trending of stability data to support the retest period/shelf-life of a drug substance/product as well as to indicate when a change to retest period/shelf-life and/or cautionary labeling statement is required. Trending must also be used as a tool to identify significant trends and recommend release alert limits when necessary.

The formulation site must take appropriate action to ensure that drug substance/ product release procedures are updated to take into account the latest stability trend analysis reports issued by the Commercial Stability Site.

post change stability data must,
when sufficient data is available, be considered to replace the reference data as the basis for setting or revising registered release limits or release alert limits.

5.4 Identification of OOTs

When new results from a stability study are available, the data must be evaluated as typical or atypical against the reference data. A visual inspection of the data, for example by using a scatter plot, may be sufficient to identify typical or atypical trends and to predict adverse trends. If a visual inspection is not sufficient, further statistical evaluation should be initiated.

It is important to take into consideration the amount of data that is being evaluated, as it may be too early in the study to have sufficient data to provide confidence that OOT predictions are accurate.

5.4.1 Atypical result

The review of individual results should be performed as soon as possible after the results have been obtained and ideally by the responsible laboratory. By doing so it is possible to either confirm an atypical result or identify the probable cause of the atypical result.

An atypical result is observed when a single result, while within specification limits, is aberrant, i.e. outside normal analytical and sampling variation as well as exhibiting a difference in the typical change over time. (See figure 1-2, appendix 1).

When an analytical result appears to be atypical during evaluation of stability data, the actions must follow the steps outlined in appendix 2. As the first step, the analytical result must be reviewed to confirm the result as atypical or due to an analytical error. If an atypical result is confirmed, the probability of an OOS must be evaluated. The minimum action required when an atypical result is identified, is to monitor the next time point. The need for adding an extra time point ahead of the next scheduled time point must also be considered.

5.4.2 Atypical trend and/or adverse trend

Examples of atypical trend situations are when one or more of the following events occur:

1. A series of results within a study show a trend that is different in comparison with the trend of other studies
2. At least two consecutive results within a study are confirmed as atypical
3. An atypical result occurs in at least two studies

Examples of atypical and adverse trends are illustrated in simple scatter plots in appendix 3.
When an atypical trend is identified, the actions must follow the steps outlined in

according to the specification, especially for parameters like degradation products and impurities.

5.4.4 Statistical evaluation

The data should be presented initially as a scatter plot, allowing simple visual inspection of the characteristics of the parameter over time. Make sure that the time axis is correct. This method can be used to identify both atypical results and atypical trends by comparison with normal/typical stability results both within and between studies.

If appropriate, the individual results or batches that are identified as atypical during visual inspection may be more closely evaluated using more sophisticated statistical methods.

Comparisons with other data at the corresponding time point or comparisons of slopes or other parameters that quantify the change rate are some examples. The model used depends on the data that is being evaluated.

5.4.5 Stability Study Alert Limits

Alert limits for stability data could be either non-statistical (absolute settings) or statistical (based on reference data). Alert limits, based on reference data, can be used as an aid in identifying atypical results or atypical trends.

When setting alert limits it is recommended that a statistical approach is used. There are several different methods, although none of them can be generally Applied.

The following items should however generally be considered:

Appropriate reference data (representative for the normal stability profile of the productôs stability indicating parameter).

Availability and amount of data. Can data from several product/package combinations be used as reference? Type of data (single, multiple, near detection limits).

Appropriate model fitted to the normal degradation profile (e.g. linear or non-linear).

Time points. When can action be taken?

Choosing a suitable level of risk (avoiding false alarms).

Logistics of implementation (different market specifications, pack sizes, strengths, time points etc.).

Adequate precision, i.e. enough decimal places to enable evaluation. Once stability study alert limits have been implemented, they must be

6.2 Appendix 2 Atypical Result investigation

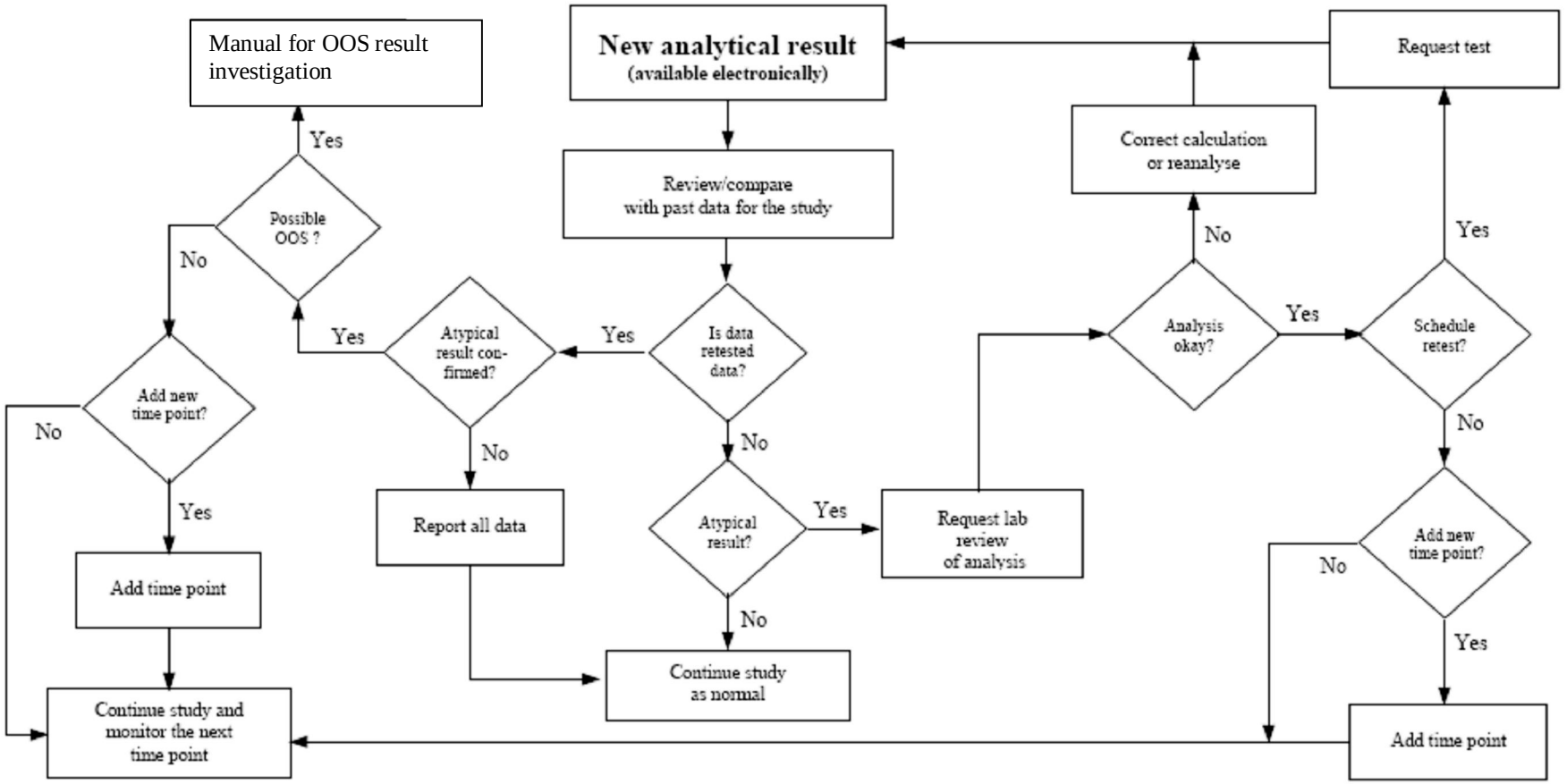

Figure 5 shows a situation where a single atypical result within a study can form a trend (in comparison with previous results within the study) that is atypical in comparison with other studies. If this single result is close to the specification limit it may be considered to be an adverse trend.

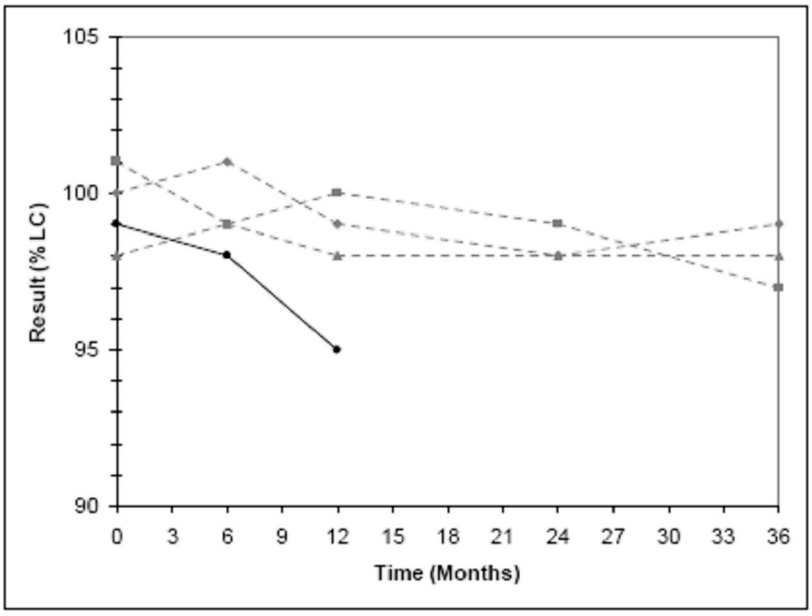

Figure 5: A single result within a study resulting in an atypical trend compared to other studies

A clearly atypical trend as shown in figure 8 might not result in an adverse trend, but since the trend is not expected, it could still be of interest for further investigation.

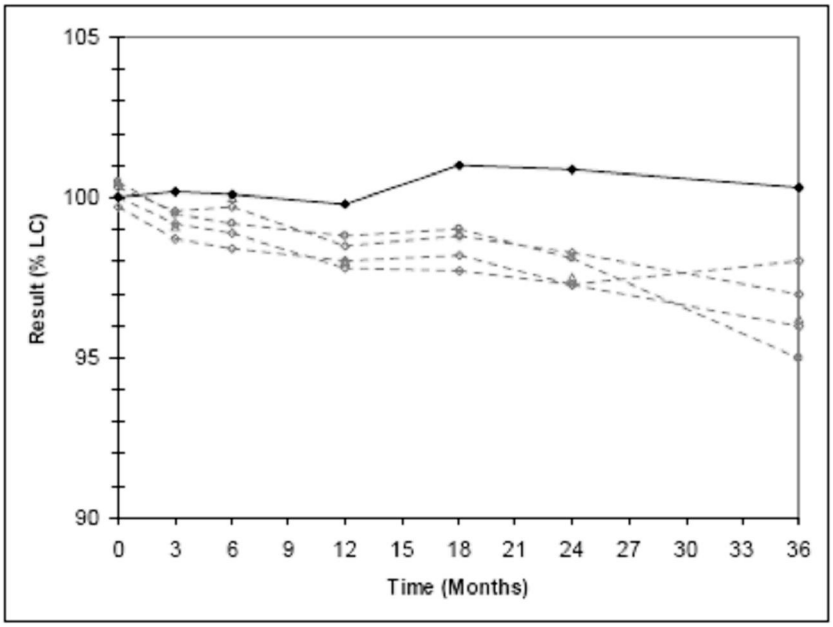

Figure 8: An atypical (but not adverse) trend

The opposite situation, not clearly atypical, but adverse trend is illustrated in figure 9. The trend is typical, but slightly worse. This is most likely to occur when the initial value for a parameter in a normal behaving stability study is near to its specification limit.

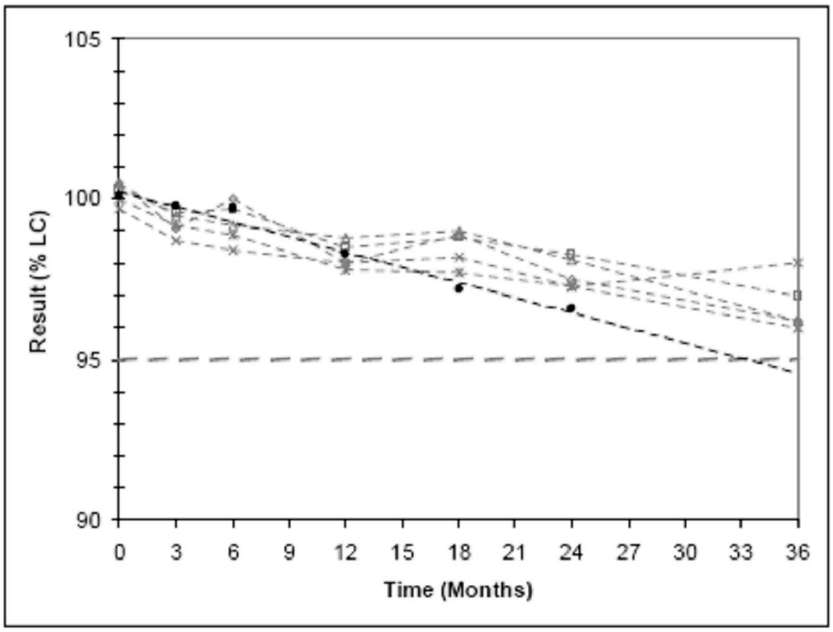

Figure 9: A not evident atypical result but possibly adverse trend

