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.

appendix 4.
According to the flow diagram in appendix 4, an assessment must be made in order to confirm whether an observed trend is adverse or not, i.e. whether there is a probability for an OOS to occur.

Studies where adverse trends have been identified must be monitored closely. Additional time points may be required before the next scheduled time point to further confirm the trend. When a trend is regarded as adverse it is important to identify the reason for the study set down (typical batch, set down due to deviation or change control).

It is also important to determine the scope of the adverse result or trend, that is to determine whether the adverse trend is isolated to one batch or whether the atypical trend is affecting many batches. In either case, an investigation must be initiated.

A detailed investigation should document the review and assessment of the data, the statistical models chosen and follow-up actions that may be required. For example, the registered release limits or release alert limits may require review to ensure that the established limits are set at an appropriate level or if changes are required as a result of the investigation. Actions may also include, but are not limited to: requesting an investigation to determine process, formulation or testing changes, new analyst, equipment or instrument changes, or deviations associated with the batch.

When an atypical trend that is not regarded as adverse is identified, the probable cause should be investigated. An example of such a case is shown in appendix 3, figure 8.

When a trend is considered as not atypical, there can still be a possible OOS, which must be assessed according to the flow diagram in appendix 4.

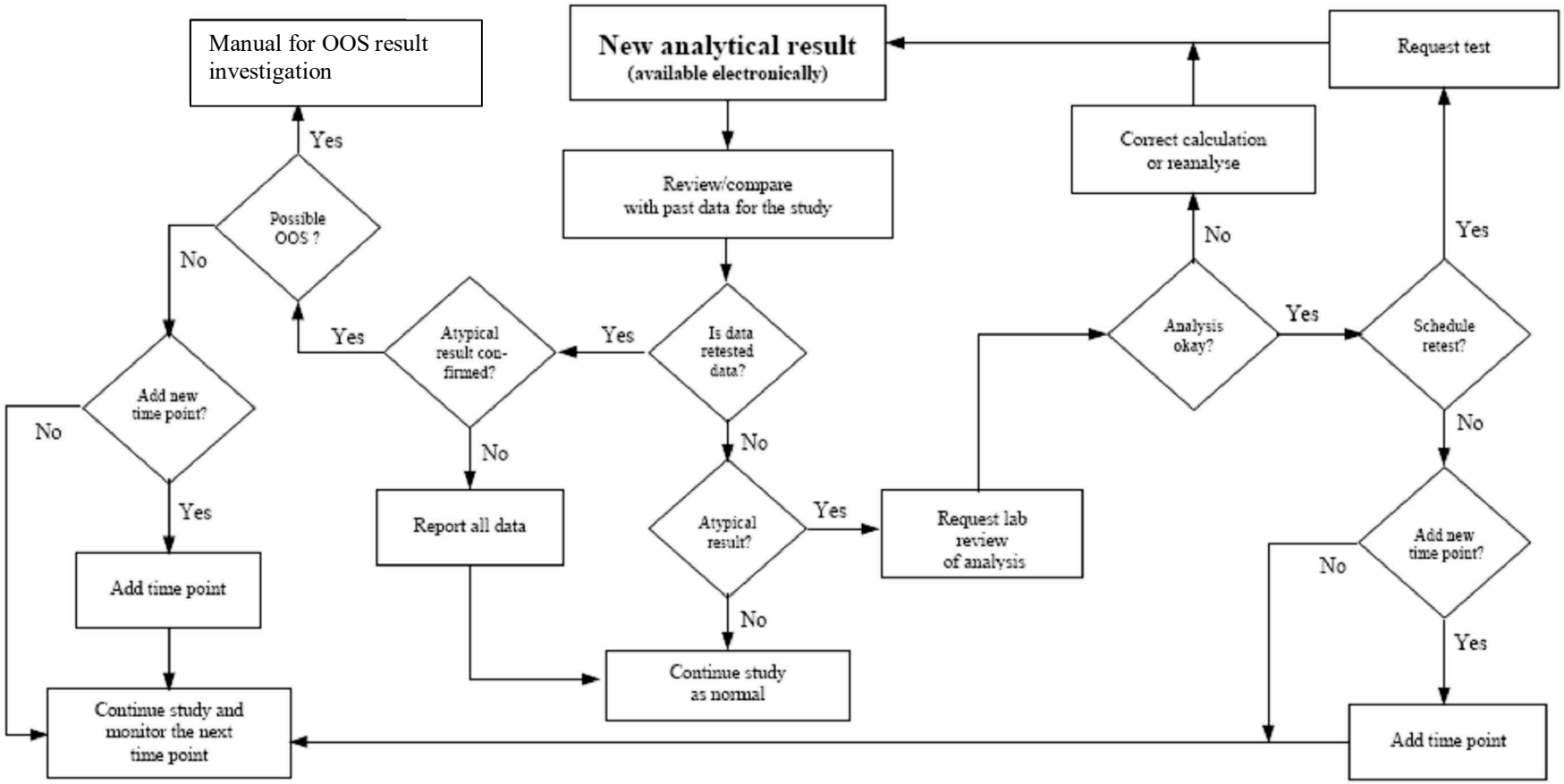
5.4.3 Compilation of reference data

Data used for OOT evaluation must be gathered and compiled electronically with adequate precision. An appropriate number of studies must be selected in order to characterize the stability profile of a parameter. As the analytical variability increases, more studies will be required to serve as reference. The reference data should be reviewed periodically and the set of data revised if required.

When results from the last time point of a study are available, an evaluation must be done regarding if to include the data from this study in the reference data. The data can be incorporated in the reference data for that product, if it is considered typical. If the data is atypical, the reason for the study set down must be identified and if necessary the cause of the atypical results be clarified.

Reference data provides a good background for precision that includes product, method and laboratory variability in order to accurately assess the trending for a particular batch. It may be necessary to include more decimals than are reported

6.2 Appendix 2 Atypical Result investigation



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.

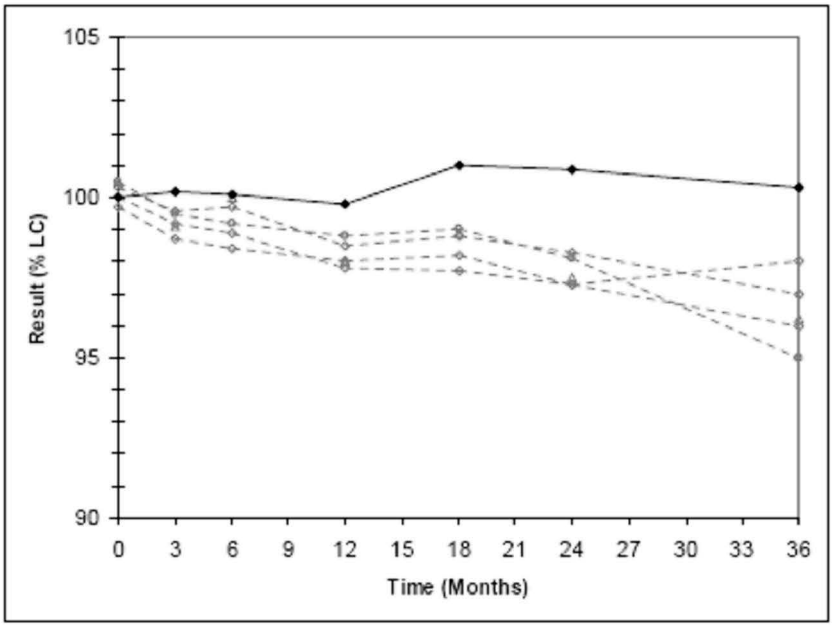


Figure 8: An atypical (but not adverse) trend

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.

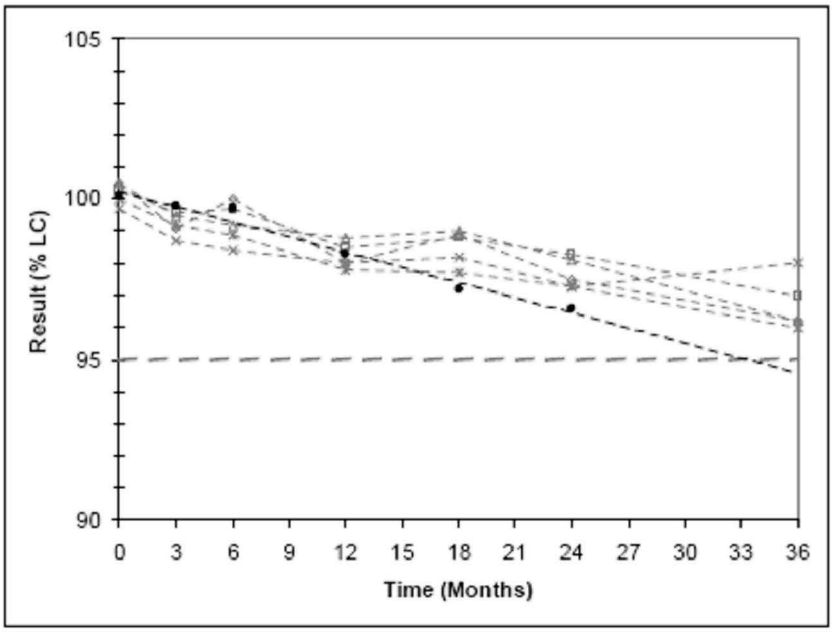


Figure 9: A not evident atypical result but possibly adverse trend

