

# Standard Operating Procedure

## Title: Method Validation Procedure

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### Procedure

#### 1. General Requirements

- 1.1. Validation of an analytical or microbiological method is the process by which it is established by Laboratory studies, that the performance characteristics of the method meet the requirements for the intended analytical applications. Methods must be re-validated if conditions are changed significantly.
- 1.2. New and revised analytical and microbiological methods are supported by sufficient Laboratory data to document the validity of these procedures. The Technical Department is responsible for ensuring that analytical and microbiological testing methods comply with the validated procedures and have been approved by the relevant authorities, before being released into either Laboratory.
- 1.3. Ideally a method should be based on established techniques requiring commonly available equipment with the greatest selectivity.
- 1.4. The validation evaluation includes the assessment of the clarity and completeness of the description of the method, the determination of the need for the method and documentation that the methods have been appropriately validated. It is essential to establish that analytical procedures produce data that are sufficiently accurate and precise for their intended purpose.
- 1.5. Revised procedures should compare the limitations of the current assay and the advantages offered by the proposed method.
- 1.6. All analytical procedures must be validated prior to generating data that is intended for regulatory submissions or that are used to test finished products, raw materials or packaging components.
- 1.7. Cleaning processes are validated to the degree appropriate to their intended use.
- 1.8. Analytical and Microbiological Method Validation should:
  1. Identify the need for the assay.
  2. Describe the capability of the specific method proposed.
  3. Provide a rationale for use of the new/modified procedure.
  4. Biological testing, for example sterility, endotoxin testing and the microbiological examination of non-sterile products are validated in line with Pharmacopoeial or other standard requirements.
- 1.9. The proposal should contain a complete description of the method in sufficient detail so a technician may replicate it with ease.

The method should include:

  1. All important operational parameters.
  2. Specific instructions e.g. preparation of reagents, media, storage of reference standards.
  3. Methodology for the performance of systems suitability tests.
  4. Descriptions of blanks used.
  5. Safety precautions.
  6. Explicit formulas for the calculation of test results.
- 1.10. Thorough and complete documentation of the method validation should be provided. The documentation should include summaries of experimental data and calculations substantiating each of the applicable analytical performance parameters.
- 1.11. Performance characteristics are expressed in terms of analytical parameters: accuracy, precision, specificity, limit of detection, limit of quantitation, robustness, linearity and range and apply to both Biological and Chemical assays.

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### 4.1.2. Determination

The accuracy of an analytical method may be determined by applying that method to samples or mixtures of excipients to which known amounts of analyte have been added both above and below the normal levels expected in the samples. The accuracy is then calculated from the test results as the percentage of analyte recovered by the assay.

## 4.2. Precision

### 4.2.1. Definition

The precision of an analytical method is the degree of agreement among individual test results when the procedure is applied repeatedly to multiple samplings of a homogeneous sample. The precision of an analytical method is usually expressed as the standard deviation or relative standard deviation (coefficient of variation). Precision may be a measure of either the degree of reproducibility or of repeatability of the analytical method under normal operating conditions. In this context, reproducibility refers to the use of the analytical procedure in different laboratories. Intermediate precision expresses within-Laboratory variation, as on different days, or with different analysts to the use of the analytical procedure within a Laboratory over a short period of time using the same analyst with the same equipment. For most purposes, repeatability is the criterion of concern in analytical procedures.

### 4.2.2. Determination

The precision of an analytical method is determined by assaying a sufficient number of aliquots of a homogeneous sample to be able to calculate statistically valid estimates of standard deviation or relative standard deviation (coefficient of variation). Assays in this context are independent analyses of samples that have been carried through the complete analytical procedure from sample preparation to final test result.

## 4.3. Specificity

### 4.3.1. Definition

The specificity of an analytical method is its ability to measure accurately and specifically the analyte in the presence of components that may be expected to be present in the sample matrix. Specificity may often be expressed as the degree of bias of test results obtained by analysis of samples containing added impurities, degradation products, related chemical compounds, or placebo ingredients when compared to test results from samples without added substances. The bias may be expressed as the difference in assay results between the two groups of samples. Specificity is a measure of the degree of interference (or absence thereof) in the analysis of complex sample mixtures.

### 4.3.2. Determination

The specificity of an analytical method is determined by comparing test results from the analysis of samples containing impurities, degradation products, or placebo ingredients with those obtained from the analysis of samples without impurities, degradation products, or placebo ingredients. The bias of the assay, if any, is the difference in test results between the two groups of samples. When impurities or degradation products are unidentified or unavailable, specificity may be demonstrated by analysis by the method in question of samples containing impurities or degradation products and comparing the results to those from additional purity assays (e.g. chromatographic assay, phase solubility differential scanning calorimetry). The degree of agreement of test results is a measure of the specificity.

## 4.4. Limit of Detection

### 4.4.1. Definition