PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

STANDARD OPERATING PROCEDURE	
Department: Quality Assurance	**SOP No.:**
Title: Analytical Method Validation of Compendial or Non Compendial Methods for Active Pharmaceutical Ingredients and Excipients	**Effective Date:**
Supersedes: Nil	**Review Date:**
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1.0 OBJECTIVE:

To lay down a procedure for Analytical Method Validation of Compendial or Non Compendial methods for Active Pharmaceutical Ingredients and Excipients.

2.0 SCOPE:

This SOP is applicable to Validate Test Method which are Compendial or Non Compendial, where Identification, Purity and Assay Test Method adopted from Scientific Literature, Technology Transfer Document or Method Development In-house Laboratory, Compendial Method may checked for System Suitability & System Precision, Specificity Placebo Interference, Method Precision, Intermediate Precision, Accuracy, Robustness, Solution Stability for Active Pharmaceutical Ingredients & Excipients in Quality Control Laboratory.

3.0 RESPONSIBILITY:

Officer / Executive QC

4.0 ACCOUNTABILITY:

Head QC

5.0 PROCEDURE:

5.1 DEFINITIONS:

- **ANALYTICAL METHOD VALIDATION:**
  Analytical Method Validation is the collection of documented evidence that an Analytical Procedure is suitable for its intended use.

- **ACCURACY:**
  The Accuracy of an Analytical Procedure is the closeness of test results obtained by that procedure to the true value. The Accuracy of an Analytical Procedure should be established across its range.

- **PRECISION:**
  The Precision of an Analytical Procedure is the degree of agreement among individual test results when the procedure is applied repeatedly to multiple samplings of a homogeneous sample.

- **SPECIFICITY:**
  The ability to assess unequivocally the analyte in the presence of components that may be expected to be present, such as impurities, degradation products, and matrix components.

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- **DETECTION LIMIT:**
  The Detection Limit is a characteristic of limit tests. It is the lowest amount of analyte in a sample that can be detected, but not necessarily quantitated, under the stated experimental conditions.

- **QUANTITATION LIMIT:**
  It is the lowest amount of analyte in a sample that can be determined with acceptable Precision and Accuracy under the stated experimental conditions.

- **LINEARITY:**
  The Linearity of an Analytical Procedure is its ability to elicit test results that are directly, or by a well-defined mathematical transformation, proportional to the concentration of analyte in samples within a given range.

- **RANGE:**
  The Range of an Analytical Procedure is the interval between the upper and lower levels of analyte (including these levels) that have been demonstrated to be determined with a suitable level of Precision, Accuracy, and Linearity.

- **ROBUSTNESS:**
  The Robustness of an Analytical Procedure is a measure of its capacity to remain unaffected by small but deliberate variations in procedural parameters listed in the procedure documentation and provides an indication of its suitability during normal usage.

- **SYSTEM SUITABILITY:**
  If measurements are susceptible to variations in analytical conditions, these should be suitably controlled, or a precautionary statement should be included in the procedure.

5.2 The most common categories for Analytical Method Validation are as follows:

5.2.1 Category-I (Assay):
Analytical Procedures for Quantitation of major components of Bulk Drug substances or Active Ingredients (including preservatives) or Excipients.

5.2.2 Category-II (For Impurities):
Analytical Procedures for determination of Impurities in Bulk Drug substances. These procedures include quantitative Assays and Limit Test.

5.2.3 Category-III:
Analytical Procedures for determination of performance characteristics (e.g., Dissolution, Drug Release).

5.2.4 Category-IV:
Identification Tests

5.3 For each category, different analytical information is needed. Elements that are normally required for each of these categories are given in point **5.7** & **5.8**.

5.4 Already established general procedures (e.g. Titrimetric Determination of Water, Bacterial Endotoxins) should be verified to establish their suitability for use, such as their Accuracy (and absence of possible interference) when used for a new product or Raw Material.

5.5 The validity of an Analytical Procedure can be verified only by Laboratory Studies. Therefore, documentation of the successful completion of such studies is a basic requirement for determining whether a procedure is suitable for its intended application(s).

5.6 Current Compendial procedures are also subject to regulations that require demonstration of suitability under actual conditions of use. Appropriate documentation should accompany any proposal for new or revised Compendial Analytical Procedures.

5.7 ANALYTICAL METHOD VALIDATION REQUIRMENTS FOR COMPENDIAL PRODUCTS:

Analytical Performance Characteristics	Category-I	Category-II		Category-III	Category- IV
		Quantitative	Limit Tests		
Accuracy	Yes	Yes	*	*	No
Precision	Yes	Yes	No	Yes	No
Specificity	Yes	Yes	Yes	*	Yes
Detection Limit	No	No	Yes	*	No
Quantitation Limit	No	Yes	No	*	No
Linearity	Yes	Yes	No	*	No
Range	Yes	Yes	*	*	No
* May be required, depending on the nature of the Specific Test.					

5.8 ANALYTICAL METHOD VALIDATION REQUIRMENTS FOR NON - COMPENDIAL PRODUCTS:

Type of Analytical Procedure	Identification	Testing for Impurities		Assay, Dissolution (Measurement only) Content / Potency
		Quantitative	Limit	
Specificity	+	+	+	+
Accuracy (Recovery)	-	+	-	+
Precision	-	+	-	+
Intermediate Precision	-	+	-	+
Robustness	-	+	-	+
Forced Degradation	-	+	-	-
Solution Stability	-	+	-	+
Filter Interference	-	+	-	+
Linearity	-	+	-	+
Range	-	+	-	+
Detection Limit	-	+	+	-
Quantitation Limit	-	+	-	-

5.9 ANALYTICAL PROCEDURE:

The Analytical Procedure refers to the way of performing the Analysis. It should describe in detail the steps necessary to perform each Analytical Test. This may include but is not limited to: the sample, the reference standard and the reagents preparations, use of the Apparatus, Generation of the Calibration Curve, use of the Formulae for the Calculation, etc.

Types of Analytical Procedures to be validated:

The discussion of the validation of Analytical Procedures is directed to the four most common types of Analytical Procedures:

- Identification tests;
- Quantitative tests for Impurities Content;

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- Limit tests for the Control of Impurities;
- Quantitative tests of the Active Moiety in samples of Drug Substance or Drug Product or other selected component(s) in the Drug Product.
- Analytical Procedures, such as Dissolution Testing for Drug Products
- Testing for Impurities can be either a Quantitative Test or a Limit Test for the Impurity in a sample. Either test is intended to accurately reflect the purity characteristics of the sample. Different validation characteristics are required for a Quantitative Test than for a Limit Test.
- Assay Procedures are intended to measure the analyte present in a given sample. The assay represents a Quantitative measurement of the major component(s) in the Drug Substance.
- For the Drug Product, similar validation characteristics also apply when assaying for the Active or other selected component (s). The same validation characteristics may also apply to assays associated with other Analytical Procedures (e.g., Dissolution).

5.9.1 The objective of the Analytical Procedure should be clearly understood since this will govern the Validation Characteristics which need to be evaluated. Typical validation characteristics which should be considered are listed below:

- Accuracy
- Precision
- Repeatability
- Intermediate Precision
- Specificity
- Detection Limit
- Quantitation Limit
- Linearity
- Range

5.9.2 The table lists those Validation Characteristics regarded as the most important for the validation of different types of Analytical Procedures.

5.9.3 This list should be considered typical for the Analytical Procedures cited but occasional Exceptions should be dealt with on a case-by-case basis.

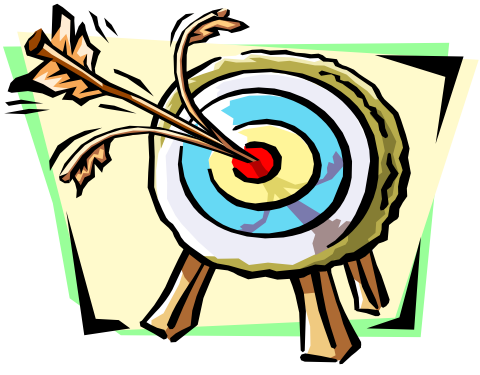
5.9.4 It should be noted that Robustness is not listed in the table but should be considered at an appropriate stage in the development of the Analytical Procedure.

5.9.5 Furthermore revalidation may be necessary in the following circumstances:

- Changes in the synthesis of the Drug Substance;
- Changes in the Analytical Procedure.

The degree of revalidation required depends on the nature of the changes. Certain other changes may require validation as well.

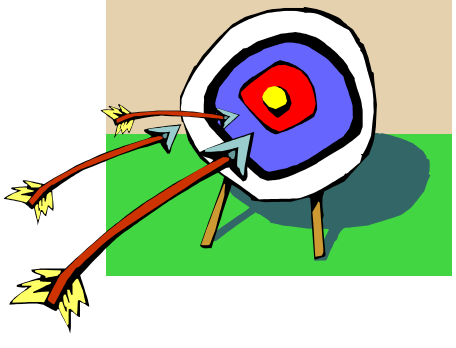
5.9.6 ACCURACY:



- The accuracy of an Analytical Procedure is the closeness of test result obtained by that procedure to the true value. The accuracy of an Analytical Procedure should be established across its range.

- Accuracy should be assessed using a minimum of nine determinations over a minimum of three concentration levels, covering the specified range (i.e., three concentrations and three replicate of each concentration).

5.9.7 PRECISION:



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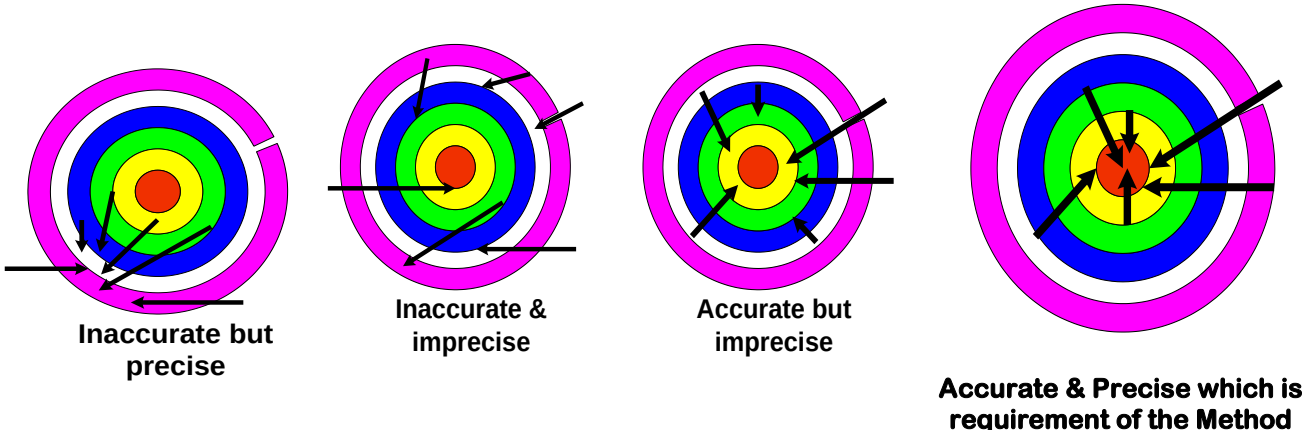
- The precision of an Analytical Procedure is the degree of agreement among individual test results when the procedure is applied repeatedly to multiple samplings of a homogeneous sample.
- The precision of an analytical procedure is usually expressed as the Standard Deviation or Relative Standard Deviation (Coefficient of Variation) of a series of measurements.
- Precision may be a measure of either the degree of Reproducibility or of Repeatability of the Analytical Procedure under normal operating conditions.
- In Reproducibility refers to the use of the Analytical Procedure in different laboratories, as in a collaborative study.
- Intermediate Precision (Also known as Ruggedness) expresses within-laboratory variation, as on different days, or with different analysts or equipment within the same laboratory.
- Repeatability refers to the use of the Analytical Procedure within a laboratory over a short period of time using the same analyst with the same equipment.
- Repeatability should be assessed using minimum of nine determinations covering the specified range for the procedure (i.e. three concentrations and three replicates of each concentration or using a minimum of six determinations at 100% of the test concentration).



5.9.8 SPECIFICITY:

- Specificity is defined as the ability to assess unequivocally the analyte in the presence of components that may be expected to be presence, such as Impurities, Degradation Products and Matrix components. Lack of specificity of an individual analytical procedure may be compensated by other supporting analytical procedure.

- International Authorities have preferred the term **"Selectivity"**, reserving **"Specificity"** for those procedure that are completely selective] For the tests discussed below, the above definition has the following implications:

- **Identification Tests**: ensures the identity of the analyte.

- **Purity Tests**:

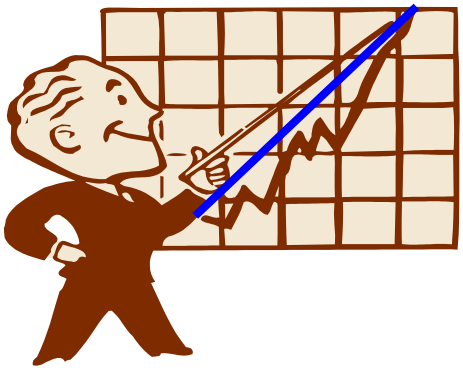
  Ensure that all the Analytical Procedures, performed allow an accurate statement of the content of Impurities of an analyte (e.g. related substances test, Heavy Metals Limit and Organic Volatile Impurities).

- **Assay:**

  - Provide an exact result, which allows an accurate statement on the content or potency of the analyte in a sample.

  - When Chromatographic Procedures are used, representative Chromatograms should be presented to demonstrate the degree of selectivity, and peaks should be appropriately labeled. Peak Purity Tests (e.g. using Diode Array or Mass Spectrometry) may be useful to show that the analyte Chromatographic Peak is not attributable to more than one component.

5.9.9 LINEARITY:



- The Linearity of an Analytical Procedure is its ability to elicit test results that are directly proportional to the concentration of analyte in samples within a give range. Thus, **"Linearity"** refers to the linearity of the relationship of concentration and assay measurement.

- In some cases, to attain linearity, the concentration and / or the measurement may be transformed. (Note that the weighing factors used in the regression analysis may change when a transformation is applied).

- Possible transformations may include Log, Square Root, or Reciprocal, although other transformation is acceptable. If Linearity is not attainable, a Nonlinear Model may be used. The goal is to have a model, whether Linear or Nonlinear, that describes closely the concentration-response relationship.

- For the establishment of Linearity, a minimum of Five Concentrations normally be used. Minimum Specified Ranges should be considered:

5.9.10 RANGE:

- The range of an Analytical Procedure is the interval between the upper and lower levels of analyte (including these levels) that have been demonstrated to be determined with a suitable level of Precision, Accuracy, and Linearity using the procedure as written.

- The range is normally expressed in the same units as test results (e.g. Percent, Parts per Million) obtained by the Analytical Procedure.

5.9.11 DETECTION LIMIT:

- The Detection Limit is a characteristic of Limit Tests. It is the lowest amount of analyte in a sample that can be detected, but not necessarily quantitated, under the stated experimental conditions. Thus, limit test merely substantiate that the amount of analyte is above or below a certain level.

- The detection limit is usually expressed as the concentration of analyte (e.g. percentage, part per billion) in the sample.

- In the case of Instrumental Analytical Procedure that exhibit background Noise is to compare measurement single from sample with known Low Concentrations of analyte with those of Blank Samples.
- The minimum concentration at which the analyte can reliably be deducted is established. Typically acceptable signals-to-noise ratios are **2:1 or 3:1.**

- Other approaches curve and the Standered Deviation of responses. Whatever method is used, the detection limit should be subsequently validated by the analysis of a suitable number of samples known to be near, or prepared at, the Detection Limit.

5.9.12 QUANTITATION LIMIT:

- The Quantitation Limit is a characteristic of Quantitative Assay for low levels of compounds in sample matrices, such as impurities in bulk drug substances.
- It is the lowest amount of analyte in a sample that can be determined with acceptable Precision and Accuracy under the stated experimental conditions.
- The Quantitation Limit is expressed as the concentration of analyte (e.g. percentage, part per billion) in the sample.
- In the case of instrumental Analytical Procedure that exhibit background noise, the ICH documents describe a common approach, which is to compare measured signal from sample with known low concentrations of analyte with those of blank samples.
- The minimum concentration at which the analyte can reliably be quantified is established. A typically acceptable signal-to-noise ratio shall be **10:1.**
- Other approaches depend on the determination of the slope of the calibration curve and the Standard Deviation of responses. Whatever approach is used, the Quantitation Limit should be subsequently validated by the analysis of a suitable number of samples known to be near, or prepared at the Quantitation Limit.

5.9.13 SAMPLE SOLUTION STABILITY:

- Solution Stability of the drug substance or drug product after preparation according to the test method should be evaluated according to the test method. Most laboratory utilize auto sampler with overnight runs and the sample shall be in solution for hours in the laboratory environment before the test procedure is completed.
- This is of concern especially for drug that can undergo degradation by hydrolysis, Photo Analysis or Adhesion to glassware.
- Recommendations**:**

- Data to support the sample solution under normal laboratory condition for the duration of the test procedure e.g. twenty-four hours should be generated.

- In exceptional cases where multiple days are needed for sample preparation or solution storage, an appropriate stability time should be selected.

5.9.14 SPECIFICITY / SELECTIVITY:

- The analyte should have no interference from other extraneous components and be well resolved from them. A representative HPLC or profile resolved should be generated and submitted to show that the extraneous peak either by addition of known compound or samples from stress testing are baseline resolved from the parent analyte.

- For the drug substance or raw material , the related substance to consider are process impurity (which include isomeric impurities) for the synthesis process, residual pesticides, solvent and other extraneous components from extracts of natural origin.

- For the drug product, the related substances may be impurities present in the active drug, degradation product, interaction of the active drug with excipients, extraneous components e.g. residual solvent from the excipients or manufacturing process, leachables or extractable from the container and closure system or from the manufacturing process.

- Representative HPLC are recommended for stressed and non stressed samples that include test method for impurity test method, the HPLC should indicate the presence of impurities at the level of chromatogram should indicate the presence of impurities at the level of Detection / Quantitation claimed. The chromatograms should be legible, labeled, and the time or time scale and attenuation should be indicated.

Points to note are as follows:

- The parent peak may be expanded e.g. by increasing the concentration. Attenuation change, so that extraneous peaks can be observed at a reasonable size to evaluate Stability indicating capability.

- The baseline should be on scale as off-scale baseline (observed as a flat straight line can hide minor peaks.) can hide minor peak.

- Peak purity can be determined by PDA detector.

- Stress Analysis should be acidic, base hydrolysis, Temperature, Photo Analysis and Oxidation.

- Non- Stress Analysis should be as per Standard Testing Procedure.

5.9.15 IDENTIFICATION: to ensure the identity of an Analyte

5.9.16 ASSAY:

when impurity are available spike the drug substance/ drugs product with appropriate level of Impurity / Excipients and demonstrate he assay not affecting there And when impurity are not available inject the test sample, prepared degradated / expired using to analysis and compare the result with our standard method

5.9.17 IMPURITY PROFILE:

When impurity available spike drug substance / drug product with appropriate level of impurity and demonstrate separation this impurity individually and form other component of complex. In case of Impurity not available, subject the test sample, prepared degradated / expire sample to analyze and compare the result with respective impurity profile.

Recommendation:

- Representative HPLC should be submitted for stressed and no stressed sample that include impurities test method, preservative(s), etc. with the related placebo sample. Representative HPLC to show selectivity by the addition of know extraneous compound.

5.9.18 SYSTEM SUITABILITY SPECIFICATION AND TESTS:

- If measurements are susceptible to variations in analytical conditions, these should be suitably controlled, or a precautionary statement should be included in the procedure. One consequence of the evaluation of robustness and ruggedness should be that a series of system suitability parameters is established to ensure that the validation of the analytical procedure is maintained whenever used.

- Typical variations are the stability of analytical solutions, different equipment, and different analysts.

- In the case of liquid chromatography, typical variations are the pH of the mobile phase, the mobile phase composition, different lots or suppliers of columns, the temperature, and the flow rate.

- In the case of Gas Chromatography, typical variations are different lots or suppliers of columns, the temperature, and the flow rate.

- Capacity Factor should be k' NMT 2

  K' = tr-to / to

  Where,

  k': Capacity factor,

  tr : Retentions time of the analyte,

  to : Elution time of the volume or non-retained components.

- Precision / Injection Repeatability (RSD) NMT 1 % of Five Injections

- Resolution (Rs) : Rs = (tr2-tr1) / (1/2)(tw1-tw2)

  Where,

  Rs = is a measure of the how well two peak are separated.

- **Tailing Factor** NMT 2 .0

  T = Wx / 2f

- **Theoretical Plate Number** (N) NLT 2000

  N= 16 (tr / tw) 2

OR new developed analytical method for new product then following parameter are to be consider in Analytical Method Validation.

- Precision
- Linearity
- Accuracy
- Range / Recovery
- Specificity
- LOD
- LOQ
- Robustness

For Officials analytical method following parameter are to consider only in Analytical Method Validation.

- Precision
- Linearity
- Accuracy / Recovery

5.9.19 **CHANGE** in brand name of product only and generic active ingredient are same and only change in strength then consider the validation of same product.

5.9.20 **OBSERVATION:**
To be clear the criticality in the method.

5.9.21 **COMMENTS AND CONCLUSION:**
HPLC Method for Drug Product:

- Methods should not be validate as a one time situation, but methods should be validated and designed by the developer or user to ensure ruggedness or robustness throughout the life of the method.
- The variation due to the drug product manufacturing process, the laboratory sample preparation procedure and the instrument performance contribute to the Accuracy of the data obtained from the analysis.
- With proper validation and tight Chromatographic Performance (System Suitability) criteria, an improvement in the reliability of the data can be obtained.

5.10 VALIDATION ELEMENTS AND ACCEPTANCE CRITERIA (CATEGORY-I):

S.No.	Validation Elements	Acceptance Criteria
1.	**Precision**	➢ The RSD of the determinations (injections) of each analyte should be NMT 2.0%
2.	**Accuracy**	➢ The average Recovery for each analyte must be NLT 98% and NMT 102% for triplicate determinations at analyte concentration of 80%, 100% & 120% of target concentration.
3.	**Specificity**	➢ No peak interference in the Placebo Injection at the retention time of target analyte. ➢ The target analyte peak is resolved from adjacent peak(s). ➢ The target analyte peak is pure by PDA analysis under Forced Degradation conditions
4.	**Method Linearity**	➢ These acceptance criteria must be met for a 5 point concentration range of at least 80% to 120% of the target concentration.

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S.No.	Validation Elements	Acceptance Criteria
		➢ The Correlation Coefficient (r) is NLT 0.995 ➢ The percentage as of Y intercept is NLT -5% & NMT 10%
5.	**Range**	➢ The Precision, Accuracy and Linearity Criteria must be met at least 80% and about 120% of sample concentration. ➢ The range is larger, report the larger range over which the acceptance criteria are met.
6.	**Ruggedness (Intermediate Precision)**	➢ The RSD of the spiked sample preparations from a second analyst, on a second instrument, and on a different day using different column must be NMT 2.0%. ➢ The RSD of the spiked sample preparations from both analyte and analysts two must be NMT 5.0%
7.	**Filter Interference (Where Applicable)**	➢ The assay of the Filtered Sample must be NLT 98.0% & NMT 102.0% relative to the same sample prepared by Centrifugation
8.	**Solution Stability (ambient or refrigerated temperature)**	➢ The Assay of the sample preparation must not change by more than 2% in a specified time period ➢ The Assay of the Working Standard must not change by more than 2% in a specified time period
9.	**Robustness**	➢ System Suitability criteria are met for the following Method Variations: ➢ Variation of Organic Component in the Mobile Phase± 5% (relative) ➢ Variation of Ion-Paring concentration of ±10%, when applicable ➢ Variation of Mobile Phase pH of ±01. pH units, when applicable ➢ variation of Flow Rate about±10% ➢ Variation of Wavelength±2nm ➢ Variation of Column Temperature about ±5^{o}C (where applicable)

5.11 VALIDATION ELEMENTS AND ACCEPTANCE CRITERIA (CATEGORY-II):

S. No.	Validation Elements	Acceptance Criteria
1.	**Precision**	➢ RSD is NMT 10.0%
2.	**Accuracy**	➢ Recovery for Target Analyte is between 90% and 110% for spiked Placebo samples for method range
3.	**Linearity**	➢ The Correlation Coefficient (r) is NLT 0.99 for the Method Range ➢ The 95% confidence interval of the intercept includes the origin. If not, the intercept is NMT 100± 10% of the response of the Standard Concentration (at the Specification Level)
4.	**Range**	➢ The concentration at which the Precision, Accuracy and Linearity Criteria are met. This Range should be from the LOQ to 150% of the Specification Level
5.	**Quantitation Limit**	➢ The Concentration at which the S/N ratio is about 10. the Quantitation Limit should be NMT the reporting threshold defined in ICH Q3B
6.	**Detection Limit**	➢ The concentration at which the S/N ratio is about 3. ➢ The Detection Limit should be NMT half of the reporting threshold defined in ICH Q3B
7.	**Specificity**	➢ No peak interference in the Placebo Injection at the retention time of Target Analyte(s). ➢ The known Impurity Peak(s) are resolved from each other and from the Active Substance Peak(s). ➢ The target Analyte peak(s) are pure by PDA analysis under Forced Degradation Conditions
8.	**Ruggedness**	➢ The Precision and Accuracy acceptance criteria for a second analyst must be met for a standard spiked Placebo Solution on a separate instrument using a different Column with sample solution prepared on a different day at the specification limit concentration level ➢ The combined RSD(s) of the Analyte(s) for both Analysts must be NMT 15.0%
9.	**Filter Interference (Where Applicable)**	➢ The peak area of each know impurity peak must be within 100±10% of Centrifuged Solution
10.	**Robustness**	➢ System Suitability Criteria are met for the following Method Variations: ➢ Variation of Organic Component in the Mobile Phase± 5% (relative) ➢ Variation of Ion-paring concentration of ±10%,

S. No.	Validation Elements	Acceptance Criteria
		where applicable ➢ Variation of mobile phase pH ±01. pH units, when applicable ➢ variation of flow rate about±10% ➢ Variation of wavelength±2nm ➢ Variation of column temperature about±5°C (where applicable)
11.	**Solution Stability**	The Assay of the Standard and sample solutions at room temperature (or refrigerated temperature) must not change by more than 5% in a specified time period at least as long as the time required to perform a typical analysis run (maximum analysis time from Sample Preparation should be defined in the Test Method).

5.12 Format for preparation of different type of Method Validation Protocols & Reports is given in current version of SOP "**Preparation, Review, Approval, Authorization, Control, Execution, Compilation, Revision & Destruction of Validation / Qualification Protocols and Reports".**

6.0 REFERENCES:

- ICH Harmonised Tripartite Guideline
- USP

7.0 ANNEXURES:

Not Applicable

ENCLOSURES: SOP Training Record

8.0 DISTRIBUTION:

- Controlled Copy No. 01 — Head Corporate Quality Assurance
- Master Copy — Corporate Quality Assurance Department

9.0 ABBREVIATIONS:

SOP	Standard Operating Procedure
No.	Number
QA	Quality Assurance
QC	Quality Control
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
LOD	Limit of Detection
LOQ	Limit of Quantification

USP	United State of Pharmacopoeia
RSD	Relative standard deviation
HPLC	High Performance Liquid Chromatography

10.0 REVISION HISTORY:

CHANGE HISTORY LOG

Revision No.	Details of Changes	Reason for Change	Effective Date	Updated By