Frontida **STANDARD OPERATING PROCEDURE**

TITLE: Validation of Analytical Procedures	
NUMBER: SOP MPC QC-RD 017-6	**CHANGE CONTROL:** CR-2667
DEPARTMENT: Quality Control and AR&D	**REVISED BY:** Susan Hua

1 Purpose:

To provide a set of general guidelines for conducting and documenting analytical method validation studies.

2 Scope:

This procedure applies to all analytical method validation studies performed by the Analytical Research & Development (ARD) and Quality Control Laboratories at Frontida BioPharm Inc., Philadelphia site.

3 References and Attachments:

3.1 USP Current Version - General Chapter <1225> Validation of Compendial Procedures

3.2 USP Current Version – General Chapter <1226> Verification of Compendial Procedures

3.3 USP Current Version - General Chapter <1092> The Dissolution Procedure: Development and Validation

3.4 FDA Center for Drug Evaluation and Research (CDER), Reviewer Guidance - Validation of Chromatographic Methods, November 1994.

3.5 Hokanson, Gerard C., A Life Cycle Approach to the Validation of Analytical Methods during Pharmaceutical Product Development, Part I: The Initial Method Validation Process, PHARMACEUTICAL TECHNOLOGY, September 1994 (118 - 130).

3.6 Hokanson, Gerard C., A Life Cycle Approach to the Validation of Analytical Methods during Pharmaceutical Product Development, Part II: Changes and the Need for Additional Validation, PHARMACEUTICAL TECHNOLOGY, October 1994 (92 - 100).

3.7 21 C.F.R. §314.70 (4-1-95 Edition)

3.8 ICH-Q2 “Validation of Analytical Procedures: Text and Methodology”

3.9 ICH-Q3A “Impurities in New Drug Substances”

3.10 ICH-Q3B “Impurities in New Drug Products”

3.11 ICH-Q3C “Residual Solvents”

3.12 U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER), July 2015, Guidance for Industry, “Pharmaceutical Quality/CMC Analytical Procedures and Methods Validation for Drugs and Biologics”

3.13 U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) CMC, Guidance for Industry INDs for Phase 2 and Phase 3 Studies, Chemistry, Manufacturing, and Controls Information

4 Responsibilities:

4.1 It is the responsibility of all analysts involved with analytical method validation to read, understand and follow this SOP. It is the AR&D analysts' responsibility to ensure that parameters specified in the HPLC or GC set-up tables in the analytical method are within the instrument's calibration/performance check parameters acceptance criteria/tolerance.

4.1.1 It is the responsibility of the Analytical Research & Development Department and the Quality Control Department to ensure that this SOP is followed.

5 Procedure:

5.1 The objective of validation of an analytical procedure is to demonstrate that the method is suitable for its intended use. The following tables summarize the method validation parameters to be validated for Drug Substances and Drug Products:

5.1.1 If the drug substance method is adopted from an official compendium, e.g., United States Pharmacopeia (USP), then no validation needs to be performed. However, a Suitability of Use, under actual conditions, needs to be verified. Verification consists of documented evidence that a previously validated method performs as intended in the intended environment.

5.1.2 If the drug substance method is adopted from a published source such as the British Pharmacopeia (BP), European Pharmacopeia (EP) etc., a Suitability of Use study needs to be verified and additional method validation studies, where appropriate, are necessary. The validations studies in this case typically include Linearity, Precision, and Specificity; however, the studies may be different depending on the intended use of the method.

5.1.3 If the drug substance method is adopted from an unpublished source such as a drug substance manufacturer or client, the available method validation data from the source must be reviewed and determined to be suitability for intended use. In addition, a Suitability of Use study needs to be verified and additional method validation studies, where appropriate, are necessary.

5.1.4 If the drug product method is adopted from an official compendium, e.g. USP, BP, and then all the validation experiments described herein need to be performed with the exception of any Linearity experiments. If extensive data is available utilizing the current method, the precision, intermediate precision, and filtration studies, accuracy, stability of standard and sample solutions, robustness, forced degradation then at the discretion of the study sponsor these studies can be waived.

Table 1
Parameters to be Validated on Procedures for Drug Substances (DS)

Procedure	Specificity	Linearity	Range	Accuracy	Precision (Repeatability)	Intermediate Precision/Reproducibility **	Detection Limit (DL)	Quantitation Limit (QL)	Robustness
Related Substances									
Quantitative	X	X	X	X	X	X		X	Δ
Limit Test	X			X*			X		Δ
Residual Solvents									
Quantitative	X	X	X	X	X	X		X	Δ
Limit Test	X			X*			X		
Assay									
Spectroscopy	X	X	X	X	X	X			Δ
Chromatography	X	X	X	X	X	X			Δ
Titration/Wet Chemistry	X	X	X	X	X	X			Δ

X – Denotes that the experiment is required
Δ - Denotes that the experiment may be needed in some cases
* - only required for 100% level
** Reproducibility is done only if Method Transfer performed during Method Validation studies

Table 2
Parameters to be Verified on Compendial Procedures for Drug Substances (DS)

Procedure	Specificity	Linearity	Accuracy	Precision (Repeatability)	Detection Limit (DL)	Quantitation Limit (QL)
Quantitative	X	X***		X		X
Limit Test	X				X	
Spectroscopy	X			X		
Chromatography	X			X		
Titration/Wet Chemistry	X			X		

X – Denotes that the experiment is required
Δ - Denotes that the experiment may be needed in some cases
* - only required for 100% level
** Reproducibility is done only if Method Transfer performed during Method Validation studies
*** Study is needed only for methods with RRF determination

Table 3
Parameters to be Verified on Manufacturer's or Client's Procedures for Drug Substances (DS) and Drug Product (DP)

Procedure	Specificity	Linearity ***	Range ***	Accuracy	Precision (Repeatability)	Intermediate Precision/Reproducibility **	Detection Limit (DL)	Quantitation Limit (QL)	Robustness***
Related Substances									
Quantitative	X	X	X	X***	X	X		X	Δ
Limit Test	X			X*			X		Δ
Residual Solvents									
Quantitative	X	X	X	X***	X	X		X	Δ
Limit Test	X			Δ *			X		
Assay									
Spectroscopy	X	X	X	X***	X	X			Δ
Chromatography	X	X	X	X***	X	X			Δ
Titration/Wet Chemistry	X	X	X	X***	X	X			Δ

X – Denotes that the experiment is required
Δ - Denotes that the experiment may be needed in some cases
* - only required for 100% level
** Reproducibility is done only if Method Transfer performed during Method Validation studies
*** Those studies can be accepted from Manufacturer's or client's method validation data only if found to be in agreement with this SOP

Table 4
Parameters to be Validated on In-house Procedures for Drug Products (DP)

Procedure	Specificity	Specificity /Forced Degradation	Linearity	Range	Accuracy	Precision (Repeatability)	Intermediate Precision/Reproducibility **	Detection Limit (DL)	Quantitation Limit (QL)	Robustness
Dissolution										
Spectroscopy	X		X	X	X	X	X			Δ
Chromatography	X		X	X	X	X	X			Δ
Degradation Compounds/Related Substances										
Quantitative	X	X	X	X	X*	X	X		X	Δ
Limit Test	X				Δ [1]			X		Δ
Residual Solvents										
Quantitative	X		X	X	X	X	X		X	Δ
Limit Test	X				Δ [1]			X		
Assay										
Spectroscopy	X		X	X	X	X	X			Δ
Chromatography	X	X	X	X	X	X	X			Δ
Content Uniformity (if procedure is different from Assay procedure)										
Spectroscopy	X		X	X	X	X	X			Δ
Chromatography	X		X	X	X	X	X			Δ

X - Denotes that the experiment is required
Δ - Denotes that the experiment may be needed in some cases
[1] for 100% level only
* Accuracy can be waived if there are insufficient quantities of impurities as deemed by Manager/ Director of ARD.
** Reproducibility is done only if Method Transfer performed during Method Validation studies.

Table 5
Parameters to be Verified on Compendial Procedures for Drug Products (DP)

Procedure	Specificity	Selectivity	Linearity	Range	Accuracy	Precision (Repeatability)	Intermediate Precision/ Reproducibility **	Detection Limit (DL)	Quantitation Limit (QL)	Robustness
Dissolution										
Spectroscopy	X		X	X	X	X	X			Δ
Chromatography	X		X	X	X	X	X			Δ
Degradation Compounds/Related Substances										
Quantitative	X	X	X***	X	X	X	X		X	Δ
Limit Test	X				Δ [1]	X		X		Δ
Assay										
Spectroscopy	X		X	X	X	X	X			Δ
Chromatography	X	X	X	X	X	X	X			Δ
Content Uniformity (if procedure is different from Assay procedure)										
Spectroscopy	X		X	X	X	X	X			Δ
Chromatography	X		X	X	X	X	X			Δ

X – Denotes that the experiment is required
Δ - Denotes that the experiment may be needed in some cases[1] for 100% level only
* Accuracy can be waived if there are insufficient quantities of impurities as deemed by Manager/ Director of ARD.
** Reproducibility is done only if Method Transfer performed during Method Validation studies
*** Study is needed only for methods with RRF determination.

Table 6

Parameters to be Considered for Re-Validation

Reason	Test	Specificity	Selectivity	Linearity	Range	Accuracy	Precision (Repeatability)	Intermediate Precision/ Reproducibility**	Quantitation Limit (QL)	Robustness
Change to API										
	Assay (DS, DP)	X	Δ							
	Related Substances (DS,DP)	X	Δ	Δ	Δ	Δ	Δ		Δ	
	Residual Solvents	X	Δ	Δ	Δ	Δ	Δ		Δ	
Change in DP Process										
	All methods	Δ					Δ			
Change in Formulation										
New Strength added	All methods	Δ		Δ	Δ	Δ	Δ			Δ
Formulation Change	All methods	Refer to Table 7								
Method Change										
Sample Preparation	All methods	Δ	Δ	Δ	Δ	Δ	X	Δ		Δ
Operating Parameters*/ Instrumentation*	All methods	Δ	Δ	Δ	Δ	Δ	X	X	Δ	Δ

X – Denotes that the experiment is required
Δ - Denotes that the experiment may be needed in some cases (for example: change in API would need selectivity, linearity and recover studies, if new impurities or residual solvents are added)
* i.e. Detector change
** Reproducibility is done only if Method Transfer performed during Method Validation studies

Table 7

Parameters to be Considered in Re-Validation

Reason	Specificity	Selectivity	Linearity	Range	Accuracy	Precision (Repeatability)	Intermediate Precision/Re-producibility*		Quantitation Limit (QL)	Robustness
Change in Formulation										
1) Excipient Grade or Different Manufacturer										
a) Functional[1]	X					Δ	Δ			
b) Non-functional[2]	X									
2) Excipient Level[3]	X	Δ			X	X	Δ			
3) Additional/New Excipient										
a) Functional	X	X[4]			X	X	X			
b) Non-functional	X	X[4]			X	X	X			

[1]Functional excipient examples: rate-controlling excipient, stabilizers, binders, disintegrants, surfactants, etc.
[2]Non-functional excipients: diluents/fillers, dyes, non-functional coating, etc.
[3]Excipient level is outside the range covered in the original validation
[4]Degradation under the condition(s) that exhibited the most degradation (for stability-indicating Assay methods)

X – Denotes that the experiment is required
Δ – Denotes that the experiment may be needed in some cases
*Reproducibility is done only if Method Transfer performed during Method Validation studies

Table 8

Parameters to be Considered for Validations Intended to Support Pilot Bioequivalency Studies

Procedure	Specificity	Linearity	Range	Accuracy	Precision (Repeatability)	Quantitation Limit (QL)
Assay	X	X	X	X	X	
Dissolution	X	X	X		X	
Related Substances	X	X	X	X[1]	X	X
Residual Solvents	X	X	X	X[1]	X	

[1]A minimum of one (1) level at 100%, three preparations, is normally required for the Accuracy study. If those criteria are not met the test will be considered a limit test.

Table 9
Parameters to be Considered for Validations Intended to Support Phase 2 Clinical Trial Studies

Procedure	Selectivity	Specificity	Linearity	Range	Accuracy	Precision (Repeatability)	Detection Limit (QL)	Quantitation Limit (QL)
Identification	X							
Assay	X	X[2]	X	X	X[1]	X		
Dissolution	X		X	X	X[1]	X		
Limit Test	X					X		
Related Substances	X	X[2]	X	X	X(At 100% of reporting threshold only)	X	X	X
Residual Solvents	X		X	X	X(At 100% level only)	X		

[1]A minimum of three (1) levels, three preparations, is normally required for the Accuracy study. If those criteria are not met the test will be considered a limit test.
[2]It is recommended

5.1.5 In addition, all validation studies, including re-validation studies (when appropriate) need to conduct stability of sample and standard solutions. Filtration studies must be conducted to qualify an alternate filter. Alternate column qualifications need to be conducted when appropriate.

5.1.6 The guidelines established in this Standard Operating Procedure were designed primarily for High Performance Liquid Chromatography (HPLC), Ultra Performance Liquid Chromatography (UPLC) and Gas Chromatography (GC) methods. However, the preceding tables list the appropriate validation experiments, which need to be conducted. For other methods not addressed in this SOP, the validity/acceptance criteria are established in the individual protocols.

5.1.7 The validity and acceptance criteria set forth in this guideline serve as default criteria for method validation protocols. The detailed requirements for each method validation study are specified in the associated method validation protocol as described in this SOP. When there are differences between an individual method validation protocol and this SOP, the protocol supersedes this guideline.

5.2 **Validation Guidelines**

5.2.1 For definitions of the terms, see the latest revision of the U.S. Pharmacopoeia/National Formulary (USP/NF).

5.2.2 For approved and submitted products, the project sponsor contacts Regulatory Affairs to determine the filing requirements.

5.2.3 For drug substance and other pure compounds, the method validation requirements are summarized in Table 1; the method verification requirements for the compendial and manufacture procedures are summarized in Tables 2 and 3. For drug product, refer to Tables 4 and 5 for method validation experiments and method verification experiments using compendial methods. For revalidation, refer to Tables 6 and 7 for method validation experiments. For method validations of method in support of pilot bioequivalency studies, see Table 8. For support of phase 2 clinical trial study refer to Table 9. Method validation is not required the methods to support the product for pre-clinical trial study and phase 1 clinical study.

5.2.4 QC/ARD Validation Protocols/Reports - The validation protocol is reviewed and approved by the Chemist, QC/AR&D Management/Designee, and QA/Designee.

The validation protocol outlines the approach to the validation of the method and establishes acceptance criteria and generally includes the following elements:

5.2.4.1 A list of the experiments planned for validation including a brief explanation of experimental objectives, experimental design, data analysis techniques, reference standards, and acceptance criteria.

5.2.4.2 If a specific test is intended to fulfill the requirements for more than one element of validation (e.g. precision and intermediate precision), it is stated explicitly in the protocol. All required elements of validation are addressed, either by validation testing or with a brief explanation of why validation testing to support that element is not needed.
The intended application of the method (e.g. in-process testing, finished finished product testing, stability testing) as well as the intended use of the method, (e.g. official regulatory method, alternate method or method improvement), including the products and strengths to be covered by the validation.

5.2.4.4 The relationship with approved or compendial methods.

5.2.5 The validation protocol includes a detailed description of the proposed analytical method.

5.2.6 The validity and acceptance criteria specified in the protocol are selected so as to demonstrate that the proposed method has adequate sensitivity, specificity, linearity, accuracy and precision for its intended use.

5.2.7 Criteria Definitions

5.2.7.1 Validity Criterion: Criteria applied to the data to determine if the data is valid. System suitability is an example of a validity criterion. Additional validity criteria are added to specific tests throughout this document.

5.2.7.2 Acceptance Criterion: Criteria applied to valid data to determine if the data are acceptable.

5.2.8 For multiple strength products or multiple formulations, it can be appropriate for a given test to cover more than one strength/formulation. These instances are addressed in the individual protocols.

5.2.9 Inclusion of conversion factor for impurity content calculation in related substances test by external standard calculation.

5.2.9.1 When the label claim for a drug product is free base, and the drug substance which used in a formulation is a salt, then in order to have the same level of impurity in the drug product as determined in the drug substance, apply the conversion factor to convert label claim from base to salt.

5.2.9.2 When an impurity standard available is in a different form than that which is present in the drug substance or drug product, then a correction factor is needed for the impurity standard to convert it into the form that is present in drug substance or drug product. In this case, the correction factor is independent of label claim.

5.2.9.3 When the impurity standard available is in a different form than that which is present in drug substance or drug product, then a correction factor is to be applied to impurity standard to convert it into the form in which it is present in drug substance or drug product. Also, the label claim for the drug product is free base, and the drug substance which used for the formulation is a salt, in order to have same level of impurity in the drug product as determined in the drug substance, it is needed to apply conversion factor for label claim from base to salt. In this case, two correction factors shall be applied, one correction factor for impurity conversion and second shall be for label claim conversion.

5.3 Specific Method Validation Tests based on HPLC, UPLC or GC

5.3.1 **System Suitability -** The goal of the system suitability test is to ensure that, at the time of testing, the instrument or system is functioning properly, and has the requisite reproducibility, sensitivity, accuracy, specificity, and/or precision to perform the intended test properly. If the collection of validation tests is not performed concomitantly, each instrumental run in the suite of validation tests is preceded by a system suitability test.

System suitability testing generally includes various measures of chromatographic performance such as reproducibility, Capacity factor (k'), Number of theoretical plates (N), resolution factor (R), and Tailing factor (T). Appropriate limits are set for the applicable parameters for the proposed analysis.

For impurity tests, a stringent resolution test is performed, if required. For example, the known impurity which elutes closest to the analyte peak is used in the resolution requirement.

5.3.2 **Linearity and Range -** The primary objective of a linearity study is to assess whether single point calibration provides sufficient accuracy over the intended range of possible concentrations or amounts expected. Typically, the linearity solutions are prepared by diluting from a single stock solution.

5.3.2.1 **Range** - The testing range to be validated is determined by verifying that the analytical procedure provides acceptable precision, accuracy, and linearity when applied to samples containing analyte at the extremes of the range as well as within the range. For finished product assay, the range is typically 50-150% of target concentration; for dissolution it is typically 10-150%. For related substances, the range is typically from the ***reporting threshold*** to 150% of the specification (refer to ICH Guidance Q3A and Q3B for reporting threshold). For residual solvents, the range is typically from the quantitation limit (QL) to at least 150% of the specification.

5.3.2.2 **Concentration Levels** - It is advisable to use at least five different standard concentrations (or amounts) to cover the specification. All other factors (e.g., solvent composition, internal standard amount) should be maintained substantially constant.

5.3.2.3 **Linearity Acceptance Criteria**

5.3.2.3.1 Unless otherwise specified in the individual protocol, the results generated from the linearity studies are analyzed as follows:

1) Plot instrument response vs. concentration (amount).

2) Perform regression analysis without forcing the line through the origin (calculate correlation coefficient, slope, and intercept and residual sum of squares).

3) Plot relative response factor vs. concentration for all points.

	Assay/CU	Cleaning Validation	Residual Solvents	Related Substances	Dissolution
Correlation Coefficient (R), NLT	0.999	0.99	0.99	0.995	0.999
Relative Response Factor (RRF)	98.0%-102.0%	80.0%-120.0%	80.0%-120.0%	80.0%-120.0%	97.0%-103.0%
Percent Y-Intercept	2%	10%	10%	10%	2%

These requirements are for quantitative tests only. If the method is not capable of meeting any of these criteria, then Frontida has the right to make the particular test a limit test.

5.3.2.4 **Relative Response Factor (RRF) of an impurity**

The Relative Response Factor (RRF) of an impurity is defined as the ratio of the peak response of the impurity to the peak response of an equal mass of the active. It should be calculated by dividing the slope of peak response of the impurity to the slope of the peak response of active in the Linearity Study.

$$\text{RRF of Impurity} = \frac{\text{Slope of Impurity from Linearity Study}}{\text{Slope of Active from Linearity Study}}$$

5.3.3 **Specificity** - The objective of testing the proposed analytical method for selectivity is to ensure that, under the conditions of analysis, no other compounds that may be present interfere appreciably with quantitation of the analyte.

For Dissolution/Drug release test performed by UV Spectrophotometric Analysis any placebo interference should not exceed 2%, compared to the standard using the formula:

$$100C_S\ (A_P/A_S)\ (V/L)$$

in which C_S is the concentration, in mg per mL, of the standard; A_P and A_S are the absorbance of the placebo/active drug or degradant and the standard, respectively; V is the volume, in mL, of the medium; and L is the label claim, in mg.

The effect of the absorbance of the blank at the analytical wavelength should be evaluated. In most cases, the absorbance of the dissolution medium blank may not exceed 1% of the standard solution at the concentration used for analysis. Values >1% must be evaluated on a case-by-case basis.

5.3.3.1 **Sample Matrix Interference (Drug Product)** - Assessment of sample matrix interference for analyses of active ingredients usually involves analyzing a sample preparation made from placebo. The placebo is formulated so that the concentration of each ingredient in the placebo sample preparation is greater than or equal to the corresponding concentration in the intended sample preparation. A single placebo preparation can be utilized for multiple strength products, which includes every excipients present in all strengths. The amount of placebo used is normally the same as the total amount of inactive components present in a sample preparation, although larger amounts (up to 10 times) can be used as a more rigorous test of the analytical method. In cases where an active ingredient can potentially interfere with the quantitation of an analyte (e.g., another active ingredient or an impurity, if available), it is necessary to include the potentially interfering active ingredient in the matrix preparation. Chromatograph in duplicate (to assure reproducibility) each solution for a run time of at least three (3) times the retention of the last eluting analyte peak. The 3x retention time rule applies only to non-gradient methods.

5.3.3.2 **Stability-Indicating Characteristics** - Assay methods intended for use on stability samples must be stability-indicating (i.e., the analytes must be free from any appreciable interference from degradation products that can be present). This is often accomplished by stressing separate portions of the finished product and placebo. In the case of products that contain multiple active ingredients, each active ingredient should also be stressed separately.

5.3.3.3 Related Substances method also must be tested for stability-indicating properties. This is often accomplished by stressing separate portions of the finished product, drug substance and placebo. In the case of products that contain multiple active ingredients, each active ingredient should also be stressed separately.

Forced degradation study of the drug substance must be available either from the vendor or performed in-house.

5.3.3.3.1 **Maximum Stress Conditions** - The information below defines the maximum stress conditions that are normally used. If little or no degradation is observed under the conditions listed, the compounds are generally considered to be stable, and there would normally be no need to use more vigorous stress conditions. If complete or nearly complete degradation is observed, then the particular stress condition causing the extensive degradation is repeated using milder conditions. Generally, a target of about 5 - 30 % degradation of the active ingredient should be achieved for at least one condition.

5.3.3.3.1.1 1.0 N hydrochloric acid (other acids can be used depending on the chemical structure of the main analyte) for 4 hours followed by neutralization with same amount of 1.0 N sodium hydroxide solution (or pH to neutrality with pH paper as acid could be consumed and an additional base degradation could occur)

5.3.3.3.1.2 1.0 N sodium hydroxide (other bases can be used depending on the chemical structure of the main analyte) for 4 hours followed by neutralization with same amount of 1.0 N hydrochloric acid solution (or pH to neutrality with pH paper as base could be consumed and an additional acid degradation could occur).

5.3.3.3.1.3 Degrade with a 3% solution of hydrogen peroxide for about 60 minutes at room temperature followed by dilution prior to injection of the solution.

5.3.3.3.1.4 Store under ambient conditions for at least one week.

5.3.3.3.1.5 Store under short-wavelength UV light for at least one week.

5.3.3.3.1.6 Store at 105°C for 3 hours or as specified in the method validation protocol

Other conditions that reasonably simulate sample aging may be employed, if necessary.

5.3.3.4 **Data Evaluation**:

Significant shoulders or other nearby degradation product peaks which overlap the analyte peak are generally unacceptable and signify that the method may not be stability-indicating. Where significant degradation product peaks are close to the analyte peak, some means of ensuring their separation is generally included in the analytical method. This can be accomplished via a system suitability test requiring a certain minimum resolution factor or minimum number of theoretical plates. If an extraneous peak, interfering with the main analyte is present at or below of the Reporting Threshold, the resolution criteria may not need to be set.

5.3.3.4.1 **Peak Purity** – For chromatographic methods, some assessment of the active analyte peak purity should normally be performed to ensure the absence of significant interference from degradation peaks. The procedure and acceptance criteria for peak purity evaluation are stated within the individual validation protocol.

5.3.3.4.2 **Internal Standard** – Where the analytical method uses an Internal Standard, the forced degradation study is performed without adding the internal standard. No degradation peak from the active ingredient or placebo should interfere with the quantitation of the internal standard.

5.3.3.4.3 **Identification of Degradation Products/Impurities** - In addition to the forced degradation studies, reference standards (where available) of degradation products/impurities that may be present during analysis are generally injected to ensure adequate separation from the analyte peak. When reference standards are not readily available, the identity of degradation products/impurities in the forced degradation studies may be determined by comparison to known (literature) spectra and chromatograms (retention times). A list of the major impurities (both known and unknown (label by RRT) generated by each condition should be included in the report.

5.3.3.4.4 Report Mass balance for information only.

5.3.3.5 **Selectivity of Internal Standards** - For methods with internal standards, the Selectivity Study is performed without the addition of the Internal Standard in order to be able to monitor any potential degradants that could potentially co-elute with the Internal Standard.

5.3.3.6 **Other Potential Sources of Interference** - Depending on the type of analysis involved, e.g., chemical derivatization of the analyte, it may be necessary to demonstrate that other potential sources of interference are absent.

5.3.3.7 **Accuracy -** This is normally measured via recovery studies at various concentrations spanning the intended range for the method. Multiple sample preparations (3 or more) at each of the concentration levels are normally prepared by spiking known amounts of analyte into the sample matrix and measuring the recovery against a standard. Any appreciable interaction between analyte and matrix or interference due to the matrix will appear as deviations in the amount of analyte recovered (found) versus the amount added. See the table below for general validity and acceptance criteria.

Accuracy of related substances is determined by ‘spiking’ the appropriate quantity of impurities onto the drug substance or the drug product at the levels indicated in the next table (if reference standards are available). For related substances and residual solvents tests, use of different processing methods for different levels of Accuracy is acceptable; the same processing method must be used for all standards and the 100% level analytes.

Accuracy Table

Parameter Evaluated	Assay	Content Uniformity	Cleaning Validation	Residual Solvents	Related Substances	Dissolution	Related substances/Residual Solvents Semi-Quantitative/ Limit Tests
Minimum Range	50-150%	70-130%	50-150%	*From QL to 150% of spec	From Reporting Threshold to 150% of spec	As appropriate	As appropriate
Validity Criteria							
% RSD between different sample preparations within the same concentration level	NMT RSD + 1.0%	NMT RSD + 1.0%	NMT RSD + 1.0%	NMT RSD + 1.0%	Below 0.2%- NMT 2X RSD Above 0.2%- NMT System Suitability RSD + 1.0%	NMT System Suitability RSD + 1.0%	N/A
Acceptance Criteria							
Mean % recovery from the matrix within each concentration level	98.0 – 102.0%	98.0 - 102.0%	70.0%- 130.0%	80-120%	Below 0.2%: 80-120%. Above 0.2%: 90.0-110.0%	95-105%	70 – 130%

These requirements are for quantitative tests only.

*For Related Substances test and Residual Solvents Test, %RSD between different sample preparations for the QL level and the acceptance criterion for the QL level (mean % recovery from the matrix within each concentration level) could be widen as per corresponding method validation protocol, if required. If the method is not capable of meeting any of these criteria, then Frontida has the right to make the particular test a limit test.

5.3.4 **Filtration -** A second aspect of accuracy that should be addressed is the effect of filtration. The intended filter type(s) should be evaluated for adsorption of analyte, breakthrough of particulate matter, and leaching of soluble filter residues. Although the latter two points are addressed by visual inspection, placebo analysis, or recovery study, as appropriate, the potential for adsorption of analyte is best measured by analyzing a centrifuged and filtered sample solution. In addition, the volume of filtrate to be discarded is determined by analyzing sequential fractions of filtrate. Refer to the Table below for the acceptance criteria.

Filtration Table

Parameter Evaluated	Assay	Dissolution/ Drug release	Content Uniformity	Related Substance
Percent Relative Recovery	98.0 – 102.0%	97 - 103%	98.0 - 102.0%	95.0 - 105.0%

5.3.5 **Precision-** The precision of an analytical method can be determined by performing replicate analyses on a homogeneous sample. This can be done either as a separate experiment, or equivalent information can be obtained by performing analysis of variance (ANOVA) on replicate analyses performed for an Intermediate Precision study. At least six preparations are needed to obtain a reasonable assessment of method precision. If no appropriate samples (i.e. no impurities or residual solvents above quantitation levels) are available for testing, spiked samples can be used for demonstration of Precision. The same sample preparations used for the 100% level of Accuracy can be used for Precision.

5.3.5.1 **Acceptance Criteria** - Acceptance criteria for method precision should be determined based on the intended use of the method and defined in the individual protocol. The following table represents typical associated precision requirements depending on the type of testing being validated.

Drug Product Assays (Not Including Uniformity Testing)	NMT 2.0% RSD
Dissolution Testing @ Q time point (IR Products)	NMT 10% RSD
Dissolution Testing (ER Products)	To perform actual dissolution profile
Related Substances/Residual Solvents	To be specified in the protocol.
Content Uniformity	AV NMT 15.0%

5.3.6 **Intermediate Precision/Reproducibility** - Intermediate Precision/Reproducibility is the ability of an analytical method to produce consistent and reliable results over the course of time and under varying testing conditions, but following the proposed analytical method exactly as written. Intermediate Precision/Reproducibility testing is usually performed by measuring the effect of changing unspecified variables (such as analysts, instruments, columns, etc.) on the analytical method. If no appropriate samples (i.e. no impurities or residual solvents above quantitation levels) are available for testing, spiked samples can be used for demonstration of Intermediate Precision/Reproducibility.

Intermediate Precision/Reproducibility testing generally involves performing replicate analyses on a homogeneous sample using different analysts, different instruments, different test dates (if possible), etc. A sufficient number of replicates under each condition are performed in order to simulate real-life analytical conditions.

5.3.6.1 **Acceptance Criteria** - Acceptance criteria between Precision and Intermediate Precision/Reproducibility is determined based on the intended use of the method and defined in the individual protocol. The following table represents typical associated Intermediate Precision/Reproducibility requirements depending on the type of testing being validated.

Drug Product Assay	NMT 2.0% Difference of the Means
Drug Substance Assay	NMT 1.0% Difference of the means
Dissolution Testing	NMT 10% Difference of the means if LT 85% dissolved; NMT 5% difference of the means if > 85% dissolved
Related Substances/Residual Solvents	To be specified in the protocol.
Content Uniformity	NMT 3.0% Difference of the Mean

5.3.7 **Range -** The range of an analytical method is the span of concentrations over which the method is linear, accurate, and precise. This is normally established by finding the span of concentrations for which linearity, accuracy, and precision have all been demonstrated. The precision across the range of concentrations is generally established in the accuracy study.

5.3.8 **Sensitivity** - This is the ability of the analytical method to detect the analyte at the lowest concentration that is meaningful, given the intended use of the analytical method. QL (quantitation limit) is defined as the lowest concentration in the validated range, with acceptable precision and accuracy under the stated experimental conditions. It is recommended to keep the QL at the same level as Reporting Threshold; otherwise, the recovery study needs to be performed at the QL level if the QL is lower than the Reporting Threshold. DL (detection limit) is only determined for semi-quantitative tests and is defined as the lowest concentration that provides a signal to noise ratio (S/N) of 3. QL is only determined for quantitative tests and is defined as the lowest concentration that provides a signal to noise (S/N) ratio of greater than 10 and a precision (RSD of multiple injections) suitable to the method.

The S/N is calculated as follows: $S/N = 2h/h_n$ in which h is the height of the peak corresponding to the component concerned; and h_n is the difference between the largest and smallest noise values observed over a distance equal to at least five times the width at the half-height of the peak and, if possible, situated equally around the peak of interest.

5.3.9 **Stability of Mobile Phase, Standard and Sample Solutions -** The stability of standard and sample solutions under normal laboratory environmental conditions (NLEC) should be determined to ensure that they are sufficiently stable to complete the analysis within a reasonable time frame. Once the stability characteristics of the solutions are determined, the expiry period and storage conditions of the solutions are generally included in the method. Time starts once the preparation is complete. Recovery is calculated relative to the t=0 value.

Stability of the Standard and Sample Solutions

	Assay/CU	Cleaning Validation	Residual Solvents	Related Substances	Dissolution
Sample Stability	The appearance of the solution at each specified time should remain the same as the original solution.		N/A	The appearance of the solution at each specified time should remain the same as the original solution.	
	98.0% to 102.0% and chromatography does not significantly change	90.0% to 110.0%		no significant changes in levels of impurities	98% to 102%
Standard Stability	The appearance of the solution at each specified time should remain the same as the original solution.				
	98.0% to 102.0% and chromatography does not significantly change	90.0% to 110.0%	90.0% to 110.0%	95.0% to 105.0%	98% to 102%

5.3.9.1 In order to justify an expiry period of within or more than 24 hours, the stability of standard and samples solutions should also be established. Solution stability study should be designed to insure 24 hours stability time point by performing study at intervals less than 24 hours. For example, solutions should be evaluated at 2, 4, 10, 18 and 24 hours.

5.3.9.2 Where an internal standard is used, its stability in the intended standard/sample preparation should be verified. The peak area ratios of the Standard/Internal Standard could not be used for the evaluation of the stability, and instead the peak area response of the standard is used. This is due to the fact that the Internal Standard used for the preparation of the fresh prepared standard solution belongs to a different Internal Standard preparation than the Internal Standard solution used in the Standard and Sample solution stability study. Since the Internal Standard works as a normalizing factor, the amount of the Internal Standard spiked in the Standard and Sample solution preparation should be identical. Only the amount of Internal Standard recovered from the Injection of the initial Standard preparation (T0) and respectively the standards from the additional time points will be evaluated.

5.3.10 **Robustness -** The evaluation for robustness is performed either during method development or method validation for Assay and Related Substances methods. It should demonstrate the ability of an analytical method to produce consistent and reliable results despite small, but deliberate variations from the specified conditions (within the analyst's control). Such parameters as column temperature, pH (if applicable) and mobile phase composition are deliberately changed from the specified parameters to test how robust the method is toward deviation from the specified conditions (see Tables below).

Robustness Study using GC Analysis

Parameters	Adjustable Range	Comments
Column		
Column Inner Diameter (GC)	Optional	The current practice is not to use an Alternate column brand, therefore, these studies are optional. However, during development work, different brand columns must be considered and conclusion why one column is chosen over another should be documented.
Film Thickness (Capillary GC)	Optional	
Particle Size	Optional	
Different Column Brand	Optional	
Different Column Lot Number	Yes	Can be done as part of Intermediate Precision/Reproducibility
Column Length	None	
Flow Rate	±10%	
Injection Volume and Split Volume	None	
Oven Temperature	±10%	
Oven Temperature Program	±20%	
Linear Velocity	±10%	
Head Pressure	±10%	
Vial Temperature	±5%	

Robustness Study using HPLC / UPLC Analysis

Parameters	Adjustable Range	Comments
Mobile Phase		
pH	±0.2	
Concentration of Salts in Buffer	±10%	Only if pH study is done at the same time and pH is within ±0.2
Ratio of Components		
Minor component in the MP (50% or less)	±10%	The change in any component cannot exceed ±10% absolute (i.e., in relation to the total mobile phase)
Detector		
Wavelength	±3 nm	Deviation from wavelength as specified in the MVP or MOT is not permitted. The wavelength study is done only to confirm that if detector itself has an error within ±3 nm; it will not have any impact on the results.
Column		
Length	Can be adjusted as much as ±70%	As per USP <621>
Inner Diameter	Can be adjusted if linear velocity is kept constant. See flow rate below.	
Particle Size	Can be reduces as much as 50%, but cannot be increased	
Flow Rate	±0.2 mL/min for HPLC ±0.05 mL/min for UPLC	When column dimensions have been modified, the flow rate can be adjusted using: $F_2 = F_1 \frac{d_2^2}{d_1^2}$ in which F1 is the flow rate indicated in the monograph, in mL/min; F2 is the adjusted flow rate, in mL/min; d1 is the column inner diameter indicated in the monograph; and d2 is the internal diameter of the column used. Additionally, the flow rate can be adjusted by ±50%.
Injection Volume	None	This study will not be done, since the concentration on the column is different from what will be validated (even if the recovery and linearity studies cover lower lever).
Column Temperature	±5°C	
Different Column Brand	Optional	This study has to be done during method development stage. If determined, that there is no other column can be used, conclusion has to be documented in the Notebook and/or in the Method Validation Protocol Introduction Section.

Robustness Study using UV Analysis

Parameters	Comments
Detector	±3 nm for any test

Analysis of various pertinent samples should be performed. Results of these tests are documented in the method development or validation reports. The acceptance criteria are defined in the individual protocol. However, typically, when these parameters are varied, the system suitability parameters must be met, the quality of the chromatography for the most highly stressed sample must be as good as under the original conditions and the peak should pass peak purity assessments (if applicable). Alternatively, the integrity of the chromatography is challenged using the selectivity solution preparation.

5.3.11 **Method Comparison/Equivalence Studies (Cross-Over Study)** - Certain conditions require the demonstration that the proposed analytical method yields results equivalent or superior to those of a designated reference method (the USP or regulatory approved method). These requirements may not apply in certain cases where there is documented justification that the proposed method has substantially greater accuracy, precision, selectivity, sensitivity, etc., and such a comparison would not be meaningful.

Typically, an equivalence study would be conducted by performing replicate analyses on one or more uniform composite samples using each of the two analytical methods. At least two determinations by each method should be performed, preferably all within a short time frame. If more than one composite sample is used, each sample must be tested by both methods.

5.3.11.1 **Comparison to Compendial Method** - Where a proposed analytical method differs substantially from the official compendial method (e.g., USP/NF or CFR), equivalence of the two methods must be demonstrated.

5.3.11.2 **New/Alternate Analytical Method -** Whenever a proposed analytical method is intended to supersede the existing regulatory method or be used as an alternate analytical method, the equivalence of the proposed analytical method must be established to (if applicable): (1) the official compendial method (e.g., USP/NF or CFR); and (2) to the existing regulatory analytical method (if the existing regulatory method differs from the official compendial method).

5.3.11.3 **Data Interpretation** - The method equivalence study determines whether any meaningful differences exist between the two methods. The acceptance criterion is defined in the individual validation protocol.

5.3.12 **Data Evaluation - Validity/Acceptance Criteria**

5.3.12.1 **Evaluation of Data for Validity -** The data is evaluated by the project sponsor for validity as defined. If any method validation data does not meet the validity criteria, a Lab Event Record will be opened. The work will be recorded in the method validation report.

5.3.12.2 **Evaluation of Valid Data for Acceptance**- Each method validation experiment is conducted according to the validation protocol for that method. If any valid data does not meet the acceptance criteria set forth in the method validation protocol or valid results could not be obtained, an investigation is performed and the findings will be described in the report; no Lab Event Record will be opened.

5.3.12.3 **Repeating Method Validation Experiments** - If the investigation finds no assignable cause for the validation test failure, the particular validation test must be repeated a minimum of three times to overcome the original data not meeting acceptance criterion. If the repeat tests meet the predetermined criteria set forth in the method validation protocol, the validation test is considered to have met the acceptance criteria. If any of the repeat tests fail to meet the predetermined criteria set forth in the method validation protocol, the validation test is considered to have failed. Regardless of whether or not the test meets acceptance criteria, an explanation of the original data and retest data must be included in the method validation report.

5.3.12.4 **Follow Up Action - Additional Method Development** - After a validation test is determined to have failed, additional method development work may be required.

After the necessary method modifications are completed, a revised or amended method validation protocol is written and approved before any further validation testing is performed for that test. If the redeveloped method is significant different from the original method, it is recommended that the protocol should be revised and the redeveloped method is incorporated in the updated protocol,

5.3.13 **Documentation**

5.3.13.1 Analytical Method Validation Testing is defined as those tests conducted pursuant to the approved Analytical Method Validation Protocol. Such testing is performed in accordance with all applicable cGMP regulations.

5.3.13.2 All analytical method validation data is recorded in dedicated laboratory notebooks in accordance with applicable laboratory procedures.

5.3.13.3 All analytical method validation data is audited by a primary qualified individual in accordance with applicable laboratory procedures.

5.3.13.4 The analytical method validation report should (1) provide notebook references for all analytical method validation data obtained pursuant to the approved method validation protocol and, (2) reference all lab event records from the procedure and any investigations.

5.3.13.5 The analytical method validation report must include any linearity plots, valid data, and sufficient representative chromatograms, spectra, or other instrument printouts to permit critical scientific review.

5.3.13.6 After all validation testing is properly recorded and audited, the analytical method validation report is signed by the individual(s) that performed the testing, the writer of the report, and the project sponsor.

5.3.13.7 The analytical method validation report is filed in an accessible yet secure location.

6 Training:

Quality Control
Analytical R & D

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STANDARD OPERATING PROCEDURE

DOCUMENT CHANGE HISTORY

TITLE: Validation of Analytical Procedures

NUMBER: SOP MPC QC-RD 017

REVISION: 6 **CHANGE CONTROL #:** CR-2667

CHANGE: Revised the references and attachments section by adding new references to FDA method validation guidelines. Updated sections 5.1.3 and 5.1.4 by adding specific informations. "Client" and "drug product (DP)" were added in the title of Table 3. A column for "Intermediate Precision/Reproducibility" is added in Table 5. Excipient from different manufacturer is added in Table 7. Updated the foot note in Table 8. New Table 9 is added for phase II clinical trial studies. Updated section 5.2.3 by adding reference to the contents of Table 9. QC department is added in section 5.2.4. Deleted Data analysis from Linearity and Range section. In section 5.3.4, acceptance criteria for related substance method is added in the filter study table. Updated step 5.3.12.4 for clarification of information. Made minor editorial changes throughout the document for clarity.

REVISION: 5 **EFF. DATE:** 08/16/19 **CHANGE CONTROL #:** CR-0941

CHANGE: Replaced the URL Pharma logo with Frontida logo and updated the entire procedure to comply with the current industry practice**.**

VERSION: 4.0 **EFF. DATE:** 08/19/15 **CCR #:** CC SOP-3681 **TRAINING LEVEL:** 2

CHANGE: In Section 5.1.8 removed "refer to section 5.2.13". Section 5.2.2.1 changed to read "The testing range to be validated is determined by verifying that the analytical procedure provides acceptable precision, accuracy, and linearity when applied to samples containing analyte at the extremes of the range as well as within the range". Under Section 5.2.2.4 in the Table updated the Dissolution column. Section 5.2.3 added "placebo" in the second sentence of the section and also in Section 5.2.3 added "The effect of the absorbance of the blank at the analytical wavelength should be evaluated. In most cases, the absorbance of the dissolution medium blank may not exceed 1% of the standard solution at the concentration used for analysis. Values >1% must be evaluated on a case by case basis". In Section 5.2.4 in the Accuracy Table changed "10-150%" to "*From LQL to 150% of spec". Also in Section 5.2.4 under the Accuracy Table added a paragraph regarding additional acceptance criteria. In Section 5.2.9 added "with acceptable precision and accuracy under the stated experimental conditions. It is recommended to keep the LQL at the same level as Reporting Threshold; otherwise, the recovery study needs to be performed at the LQL level if the LQL is lower than the Reporting Threshold". In Sections 5.2.13.1 and 5.2.13.2 changed "Deviation/LIR" to "Lab Event Record". Section 5.2.14.4 changed "deviation" to "lab event records". Minor editorial changes made

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VERSION: 3.0 **EFF. DATE:** 04/01/15 **CCR #:** CC SOP-3411 **TRAINING LEVEL:** 2

CHANGE: In the Purpose Section, updated Tables 1, 4, 6, 7 and 8, added notes under each Table and added new Tables 2, 3 and 5. Section 3.1 changed "Validation of Compendial Methods" to "Validation of Compendial Procedures". Section 3.2 added the reference of USP Current Version Chapter <1226> Verification of Compendial Procedures. References and Attachments Section removed the reference of Attachment A: Table of the general types of tests and the corresponding validation guidelines. Responsibility Section updated the Responsibility of the AR&D analysts. Section 5.1.1 removed "A table of the general types of tests (e.g. Assay) and the corresponding validation guidelines are listed in Attachment A. Updated Section 5.1.3 to add the references to the new Tables and updated the reference for the Table numbers. Section 5.1.4 changed ARD Validation Protocols to ARD Validation Protocols/Reports and added Director of Quality/Designee. Section 5.1.8 added "refer to section 5.2.13. Added new Section 5.1.9 and subsections. Section 5.2.2.1 added "For residual solvents, the range is from the linear quantitation limit (LQL) to at least 150% of the specification". Added new Section 5.2.2.5. Section 5.2.3 moved the second paragraph to a new Section 5.2.3.4. Added new step 5.2.3.3.1.6. Revised Section 5.2.3.5 for Selectivity of Internal Standards. Updated Section 5.2.4 and modified the Accuracy Table. In the Table under Section 5.2.6.1 added "Dissolution Testing (ER Products)". Revised Section 5.2.7 and 5.2.7.1. Section 5.2.10 updated the "Stability of the Standard and Sample Solutions" table and revised the second paragraph of the section. Added new Tables in Section 5.2.11 for Robustness Study guidance. Made minor editorial changes throughout the document. Removed Attachment A.

VERSION: 2.0 **EFF. DATE**: 10/21/13 **CCR #:** CC SOP-2819 **TRAINING LEVEL:** 1

CHANGE: Revised the purpose section. LIR is added on steps 5.2.13.1 and 5.2.13.2. Replaced CMS –C with QC or QCTS throughout the document. Editorial changes were made for clarity.

VERSION: 1.0 **EFF. DATE:** 10/01/12 **CCR #:** CC SOP-2185 **TRAINING LEVEL:** 0

CHANGE: Added "MPC" prefix to SOP number QC-RD 017 and transferred SOP to the MPC library as version 1.0. This new SOP replaces SOP QC-RD 017-5.0 in the SOP Library. No changes were made to the content of the SOP, no training is required.

VERSION: 5.0 **EFF. DATE:** 03/12/12 **CCR L #:** CC SOP-1784 **TRAINING LEVEL:** 0

CHANGE: Version 4.0 was published but on the final version (PDF version) one blank page was generated. Version 5.0 is created to re-publish the SOP to remove the blank page. No changes were made to the content of the SOP and no training is required on this version (5.0).

VERSION: 4.0 **EFF. DATE:** 03/05/12 **CCR #:** CC SOP-1784 **TRAINING LEVEL:** 2

CHANGE: Revised the Purpose section by removing the last sentence. Updated Table 2 in the Purpose section. Updated the titles of ARD Personal involved in the review and approval of protocols in the Procedure

section. Removed duplication of a sentence in the Procedure section. Updated Step 5.1.1 by removing "Categories" and also removed "Categories" in Accuracy Table. Updated Step 5.2.1 added "if required". Added a paragraph for Dissolution/Drug release test. Removed the sentence for storing under white light for at least one week. Removed "validity and" from Step 5.2.5 and updated the Table headings. Updated Step 5.2.10 and several discrepancies in Attachment A. Minor editorial and formatting changes were made throughout document for clarity.

VERSION: 3.0 **EFF. DATE:** 02/22/10 **CHANGE CONTROL #:** CC SOP-516

CHANGE: Revised section I on page 15 of 18, by adding "The S/N is calculated as follows: S/N = 2h/hn in which h is the height of the peak corresponding to the component concerned; and hn is the difference between the largest and smallest noise values observed over a distance equal to at least five times the width at the half-height of the peak and, if possible, situated equally around the peak of interest". Replaced the Mutual logo with URL Pharma logo and removed the company name and address from top of the first page.

VERSION: 2.0 **EFF. DATE:** 07/08/09 **CHANGE CONTROL #:** CC SOP-125

CHANGE: CMS department is added to the scope of the SOP.

VERSION: 1.0 **EFF. DATE:** 02/23/09 **CHANGE CONTROL #:** CC SOP-001

CHANGE: SOP Reformatted for PharmaReady DMS, no changes were made to the content. Alpha Version changed to Numeric Version (1.0)

DOC ID: D **DCRF#:** 7303 **EFFECTIVE DATE:** 04/01/08 **SUPERSEDES:** 04/05/07

CHANGE: Purpose: add validation information to 1st paragraph and Verification information to 2nd and 3rd paragraphs and add a new paragraph, "If the drug substance method is adopted etc.,,,). Table 1: add Intermediate Precision, Detection Limit, and Linear Quantitation Limit. Table 2: add Detection Limit and Linear Quantitation Limit. Add Tables 3, 4, and 5. Procedure: Validation Guidelines: step C changed raw materials to drug substance and add add steps for revalidation. Added UPLC to Specific Method Validation Tests based on HPLC or GC. Rewrote section "Range" and add solvent composition, etc. to Concentration Levels. Change table for Validity Criteria to Linearity Validity Criteria and added columns. Sample Matrix Interference: add "The 3x retention time, etc.,". Added step for Related Substances. Maximum Stress Conditions: expanded 1. and 2. Identification of Degradation Products/Impurities: add last sentence, "A list of the major impurities, etc.". Added new columns to Accuracy Table. F. Precision: add add'l information. Made adjustments to tables for Acceptance Criteria. Add table for Stability of the Standard and Sample Solutions. Added information to Robustness, Evaluation of Data for Validity, Evaluation of Valid Date for Acceptance, Repeating Method Validation Experiments, and References. Added Technical Services/QE to Training.

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STANDARD OPERATING PROCEDURE

DOC ID: C **DCRF#:** 6869 **EFFECTIVE DATE:** 04/05/07 **SUPERSEDES:** 05/18/05

CHANGE: IV.1.E. add "/Designee" to VP/Quality or VP/R&D. IV.2.B.1.: add "or the use of other approaches should be justified"

DOC ID: B **DCRF#:** 5423 **EFFECTIVE DATE:** 05/18/05 **SUPERSEDES:** 01/14/02

CHANGE: Add "selectivity" to Table 2 and 3. IV. 1.E. change Lead Chemist to Group Leader. IV.C.2.a.3. delete "The degradation conditions should be designed so that the ratio of hydrogen peroxide to active is at least ten (10) to one (1) on a mole basis. If the sample does not degrade to any appreciable extent, at least 10%, then the sample may be heated for an appropriate amount of time." IV.C.2. delete "Short Columns". C.E. delete three columns from Table for the validity and acceptance criteria. IV. F. add "Content Uniformity" to Acceptance Criteria table. M.3. delete "out-of-specification (OOS) result and replace with "data not meeting acceptance criterion." Add Compliance Group to Training section.

Doc ID: A **DCRF#:** 3995 **EFFECTIVE DATE:** 01/14/02 **SUPERSEDES:** 02/08/00

CHANGE: Replace QC/RD 013 with QC 170_00 and RD 040_00. IV.1.E: Add Assistant Director and VP Quality or VP R&D. Validity Criteria: Change check standard to ± 10.1%, change % difference to % RSD. General Validity and Acceptance Criteria Table: Delete column for Assay Category 3. Change NMT from 5.0% to 6.0 for % RSD. Acceptance Criteria Table: change % RSD to % Difference, add Content Uniformity. References: change USP 23/NF 18 to USP 24/NF 19.

DOC ID: QC/RD 017 **CC#** 3509 **EFFECTIVE DATE:** 02/08/00 **SUPERSEDES:** QC 113A

CHANGE: QC 113A was updated to QC/RD 017 to reflect the current regulatory and industry standards.

Signature Manifest

Document Number: SOP MPC QC-RD 017 **Revision:** 6
Title: Validation of Analytical Procedures

All dates and times are in Eastern Time.

SOP MPC QC-RD 017 5 Validation of Analytical Procedures

Step 4 QA Approval

Name/Signature	Title	Date	Meaning/Reason
Kirit Patel (KPATEL)	Director - QA	19 Oct 2020, 01:15:02 PM	Approved

P Step 4 Department Approval

Name/Signature	Title	Date	Meaning/Reason
Shiying Tian (STIAN)	Director, AR&D	19 Oct 2020, 02:03:17 PM	Approved
Naresh Patel (NPATEL)	Director QC	20 Oct 2020, 04:53:27 PM	Approved

P Step 4 Author Approver

Name/Signature	Title	Date	Meaning/Reason
Susan (Xiao Quig) Hua (SHUA)		19 Oct 2020, 09:32:13 PM	Approved

Step 6 Set Release Date

Name/Signature	Title	Date	Meaning/Reason
Judith Roscioli (JROSCIOLI)		19 Jul 2021, 03:39:10 PM	Approved