***ADARE PHARMA SOLUTIONS***

845 Center Drive

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METHOD VALIDATION PROTOCOL

MIXED AMPHETAMINE SALTS FORMULATION

PROTOCOL NUMBER: PE577-VP1-Rev. 0

This protocol is for the validation of the analytical procedures of Mixed Amphetamine Salts formulations (PE572 and PE577), and its intermediates (PE570, PE571, PE573, PE574, PE575, PE576). The signatures below indicate approval of this protocol:

|  |  |  |
| --- | --- | --- |
| **FUNCTIONAL AREA** | **REQUIRED APPROVALS** | **DATE** |
| **AUTHOR/ORIGINATOR** | Name: Jeffrey J Hargrave |  |
| Signature: |
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| **QUALITY CONTROL** | Name: Curtis Schreier |  |
| Signature: |
| **QUALITY ASSURANCE** | Name: Kathy Regelski |  |
| Signature: |

**EFFECTIVE DATE**:

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1. SCOPE

The method validation encompasses the following formulation with item codes:

|  |  |
| --- | --- |
| Product Name | Item Code |
| Mixed Amphetamine salts, IR Pellets – Drug layering | PE570 |
| Mixed Amphetamine salts, IR Pellets – Top coating | PE571 |
| Mixed Amphetamine salts, IR Pellets | PE572 |
| Mixed Amphetamine salts, DR Pellets – Drug layering | PE573 |
| Mixed Amphetamine salts, DR Pellets – Seal coating | PE574 |
| Mixed Amphetamine salts, DR Pellets – Eudragit L coating | PE575 |
| Mixed Amphetamine salts, DR Pellets – Top coating | PE576 |
| Mixed Amphetamine salts, DR Pellets | PE577 |

Additionally, the validation is applicable to any item code that is a packaged version of the bulk listed in the Scope section.

1. SUMMARY

This protocol provides a description of the experimentation, statistical analysis and acceptance criteria used in the activities for completion of the validation of test procedures for the determination of identification, assay, chiral method, drug release (dissolution), degradation products analysis, and moisture analysis by Karl Fischer titration, analysis for Mixed Amphetamine salts formulations and its intermediates. The designation “APT-5163” may be used within the document or subsequent report to represent the project.

Initial method validation activities were completed by Recipharm. The activities were summarized multiple method validation reports (i.e. VA 017 version 01, VA 046 version 01, VA 061 version 01, and RT DF153-04 version 01). The forced degradation experimentation and results were summarized in Report #RT DF153-04 version 01, “DF153: Stressed Degradation Study Report”. The following tables summarize the results of Recipharm’s method validation activities:

* 1. Amphetamine Assay / Content Uniformity Methodology

|  |  |
| --- | --- |
| Method Parameter | Conclusions |
| Analytical Range | 0.2mg/mL to 1.8mg/mL amphetamine base (70% of 5-mg strength content uniformity to 120% of the assay concentration) |
| Solution Stability | Standard: 5 days @ 20˚C & 5˚C  Sample: 5 days @ 20˚C & 5˚C |
| Notes | Results generated using 3-point standard calibration curve |

Report #VA 046 version 01, “Validation Report for the Assay and Degradation Product Method of Amphetamine Formulations in Accordance with MTH 1058”

* 1. Dissolution Methodology

|  |  |
| --- | --- |
| Method Parameter | Conclusions |
| Analytical Range | 0.1N HCl: 0.21mg/L (5% of 5-mg dose) to 30mg/L (120% of the 30-mg dose) expressed in amphetamine base (0.4mg/L to 48mg/L in amphetamine salts)  pH 6.0 medium: 0.16mg/L (5% of 5-mg dose) to 38mg/L (120% of the 30-mg dose) expressed in amphetamine base (0.3mg/L to 48mg/L in amphetamine salts) |
| Solution Stability | Standard: 7 days @ 20˚C & 17 days @ 5˚C  Sample: 3 days @ 20˚C in both media |
| Notes | The interaction of the standard preparation and the chromatography was equivalent regardless of the media |

Report #VA 017 version 01, “Validation Report for the Dissolution Method of Amphetamine Salts in Accordance with MTH 1022”

* 1. Degradation Analysis Methodology

|  |  |
| --- | --- |
| Method Parameter | Conclusions |
| Analytical Range | Pyrole-2-carboxilic acid: 1.2g/mL to 18g/mL (0.08% to 1.2% of the assay concentration of 1.5mg/mL as amphetamine base; 0.05% to 0.75% of the assay concentration of 2.4mg/mL as amphetamine salts)  PPCA: 1.2g/mL to 18g/mL (0.08% to 1.2% of the assay concentration of 1.5mg/mL as amphetamine base; 0.05% to 0.75% of the assay concentration of 2.4mg/mL as amphetamine salts)  Unknowns: 1.2g/mL to 18g/mL (0.08% to 1.2% of the assay concentration of 1.5mg/mL as amphetamine base; 0.05% to 0.75% of the assay concentration of 2.4mg/mL as amphetamine salts) |
| RRT & RRF | See section 8.0 |
| Quantitation Limit | Unknowns: 0.1% |
| Detection Limit | Unknowns: 0.03% |
| Notes | Results generated using 5-point standard calibration curve |

Report #VA 046 version 01, “Validation Report for the Assay and Degradation Product Method of Amphetamine Formulations in Accordance with MTH 1058”

1. PURPOSE

The purpose of this document is to describe the details of the experimental procedures, statistical analysis procedures and acceptance criteria used to validate the analytical methodology for the analysis of Mixed amphetamine salts formulations and its intermediates. The parameters listed in this validation protocol were developed using ICH guidelines1,2, USP <1225> Validation of Compendial Procedures, Adare Pharmaceuticals internal SOP # SOP-00026 and the additional references listed in the Reference section.

1. VALIDATION PARAMETERS
   1. Amphetamine Assay Methodology

Equivalency of the results using single standard versus calibration curve

Intermediate Precision

Robustness

* Solution Stability
* Extraction Efficiency
* Filter Study
* 5 Factor / 8 Experiment Design of Experiments
  1. Amphetamine Chiral Assay Methodology

Accuracy

Repeatability across the Range

Repeatability

Intermediate Precision

Specificity - Placebo Interference

Linearity

Range

Robustness

* Solution Stability
* Extraction Efficiency
* Filter Study
* 5 Factor / 8 Experiment Design of Experiments
  1. Dissolution

Intermediate Precision

Robustness

* Solution Stability
* Filter Study
* 5 Factor / 8 Experiment Design of Experiments
  1. Degradation Products Analysis

Accuracy

Repeatability across the Range

Repeatability

Specificity - Placebo Interference

Linearity

Range

Quantitation Limit

Detection Limit

Robustness

* Solution Stability
* Filter Study
* 5 Factor / 8 Experiment Design of Experiments
  1. Moisture Analysis by Karl Fischer Titration

Intermediate Precision

Robustness – Extraction Efficiency

* 1. Particle Size Distribution by Light Diffraction Measurement

Intermediate Precision

Microscopic Confirmation

* 1. Identification by HPLC RT and UV Spectra

Specificity – Interference

Intermediate Precision

1. ANALYTICAL PROCEDURES

Validation of the analytical procedures listed below will be performed using the conditions described in the Test Methodology found in Attachment #1 of this protocol.

Amphetamine Base Assay Methodology

Amphetamine Chiral Assay Methodology

Dissolution Methodology

Degradation Product Analysis Methodology

Moisture Analysis by Karl Fischer Titration

Particle Size Distribution by Light Diffraction Measurement

Identification by HPLC RT and UV Spectra

1. DEVIATION PLAN FOR THE PROTOCOL

Any deviations from the protocol will be addressed in the Method validation report. All results that are generated that fall out of the Acceptance Criteria will be addressed in the Method Validation Report and any additional validation experimentation will be included therein.

1. PRINCIPLES OF THE METHODS
   1. Assay for final product and in-process pellets

The Assay methodology is an HPLC methodology using C-18 column technology to separate Amphetamine base from the sample matrix with UV detection. The chromophores in Amphetamine molecule cause a deflection in the baseline of the chromatogram and the resulting peak is integrated and the peak area is compared to the peak area of a standard with a known concentration to determine the sample concentration.

* 1. Chiral separation of Mixed Amphetamine salts

The chiral separation is an HPLC methodology using a specified chiral column technology to separate the Dextroamphetamine and the Levoamphetamine from each other and the sample matrix with UV detection. The chromophores in optically active portions of the amphetamine molecule causes a deflection in the baseline of the chromatogram and the resulting peak is integrated and the peak area is compared to the peak area of a standard with a known concentration to determine the sample concentration.

* 1. Dissolution

The dissolution methodology uses USP 2 Apparatus (Paddles) for the immediate release pellets with 0.1N HCl as the dissolution media stirring at 50 rpm for up to 2 hours to extract Amphetamine from the sample matrix.

The dissolution methodology uses USP 2 Apparatus (Paddles) for the DR pellets and combined pellets (IR and DR) with 0.1N HCl initially and then modified to pH 6.0 for the remaining time out to 5 hours. The resulting samples are analyzed using the HPLC methodology.

* 1. Degradation Product Analysis

The degradation product analysis is an HPLC methodology using C-18 column technology to separate the known degradation products / impurities and amphetamine from the sample matrix with UV detection. The chromophores in the materials of interest cause a deflection in the baseline of the chromatogram and the resulting peak is integrated and adjusted with a relative response factor and the adjusted peak area is compared to the peak area of a standard with a known concentration to determine the sample concentration.

* 1. Moisture Analysis

The percent water in the sample is analyzed by Karl Fischer titration. During moisture analysis using a Karl Fischer apparatus, the Karl Fischer reagent, containing iodine, sulfur dioxide, a pyridine-like substance, and methanol, reacts with water according to the equation:

C5H5N•I2 + C5H5N•SO2 + C5H5N + **H2O** → 2C5H5N•HI + C5H5N•SO3

* 1. Particle Size Distribution by Light Diffraction

The laser light diffraction technique used for the determination of particle-size distribution is based on the analysis of the diffraction pattern produced when particles are exposed to a beam of monochromatic light. Historically, the early laser diffraction instruments only used scattering at small angles. However, the technique has since been broadened to include laser light scattering in a wider angular range and application of the Mie theory, in addition to the Fraunhofer approximation and anomalous diffraction.

A representative sample, dispersed at an adequate concentration in a suitable liquid or gas, is passed through a beam of monochromatic light, usually a laser. The light scattered by the particles at various angles is measured by a multi-element detector. Numerical values representing the scattering pattern are then recorded for subsequent analysis. These scattering pattern values are then transformed, using an appropriate optical model and mathematical procedure, to yield the proportion of total volume to a discrete number of size classes, forming a volumetric particle-size distribution.

* 1. Identification

The analysis of the identity of amphetamine in the product is determined by a comparison of the retention time of the major peak in the sample to the major peak in the standard chromatogram using the assay chromatography.

1. DEGRADATION PRODUCTS (RRT & RRF)

|  |  |  |  |
| --- | --- | --- | --- |
| **ID** | **RRT** | **Degradation Product Name** | **RRF** |
| 1 | 0.58 | pyrrole 2 carboxylic acid | 91 |
| 2 | 2 peaks coeluted  0.61-0.64 | 1H-Pyrrole-2,5-dicarboxylic acid | 61 |
| 3 | 0.66 | 2-(2-carboxy-1H-pyrrol-1-yl) succinic acid | 30 |
| 4 | 2 peaks coeluted  0.70-0.72 | 1-(1,2-dicarboxyethyl)-1H-pyrrole-2,5-dicarboxylic acid | 29 |
| benzaldehyde | 1.30 | benzaldehyde | 79 |
| 5 | 2.01 | 1-(1-phenylpropan-2-yl)-1H-pyrrole -2,5 dicarboxylic acid | 25 |
| 6 | 2.08 | 5-(hydroxymethyl)-1-(1-phenylpropan-2-yl)-1H-pyrrole-2-carbaldehyde | 18 |
| PPCA | 2.4 | 1-(1-phenylpropan-2-yl)-1H-pyrrole-2-carboxylicacid) | 37 |

Report #VA 061 version 01, “Validation Report Addendum for the Amphetamine Degradation Product Response Factors Determination in Amphetamine Formulation in Accordance with MTH 1058”

1. EXCIPIENTS FOR PLACEBO

Sugar Spheres

Hypromellose

Opadry White (03A280001)

Eudragit L30D 55

Triethyl Citrate

Talc

1. EXPERIMENTAL PARAMETERS FOR ASSAY METHODOLOGY

The validation experimentation in this section will utilize the components of both the IR and DR pellets to represent the final product. The results for the experimentation will validate both types of pellets individually along with the mixture because the experimentation represents worse case regarding complexity of the matrix.

The extraction efficiency studies will be completed before the intermediate precision studies to validate the proper stir time. Experiments will be combined to increase laboratory efficiencies.

| **Assay Parameter** | **Experimental Conditions** | **Acceptance Criteria** |
| --- | --- | --- |
| Equivalency of the results using single standard versus calibration curve | Six samples (n=6 from intermediate precision may be used) will be prepared following the method. The results will be generated using the single standard at 1.5 mg/mL amphetamine base and a three-point calibration curve with concentrations of 1.2, 1.5, 1.8 mg/mL Amphetamine base.  The two one-sided test (TOST) will be used to evaluate equivalency. | The upper and lower confidence interval will be ± 3% |
| Intermediate Precision | Both Analysts will complete the following on separate days and using separately made solutions:  Assay six separate preparations of a single preparation of a 1:1 mixture of the Amphetamine IR2:FC Pellets and Amphetamine DR:FC pellets with an equivalent dose of 30mg amphetamine mixed salts. The samples will be prepared by following the assay preparation procedure for 30mg strength.  The %RSD of the six results, in % label claim, will be used to determine the sample repeatability. The Confidence Interval (=0.05) for the Sample Precision will be reported. | For each Analyst:  The methodology will be considered precise if the RSD of the six assay % label claim values is NMT 2.0%  The individual results must meet acceptance criteria of the product.  Comparison of Analyst A to B:  The difference between the two means (n=6) generated by the two analysts is ±2.5%. |
| Robustness - Extraction Efficiency | To examine the Extraction efficiency of the sample preparation, a total of fifteen samples from the same lot of Amphetamine DR:FC Pellets will be mixed at differing times. Sample preparation will follow the testing method procedure for the 30mg capsule, except the following mixing time will be studied.  The solution is sonicated at the following times: 15 minutes (n=3), 30 minutes (n=3), 45 minutes (n=3), and 60 minutes (n=3). Three additional samples will be prepared that are stirred at least 12 hours and used as an infinity time point. After the initial mixing, the samples will be prepared following the method.  To determine the proper stir time, the average % Recovery of each stir time will be compared to the average % Recovery of the infinity stir time samples by using the % Difference. Trends and absolute differences will be evaluated, and an appropriate extraction time will be established. | Infinity Time Point:  Mean will be with ±2.0% of the expected % recovery and the %RSD of the three values is NMT 2.0%.  % Difference from the Infinity time point:  Individual values: ±3.0% absolute  Mean values (time point): ±2.0% absolute |
| Robustness - Solution Stability | 1. Standard Stability   Prepare a standard solution at the nominal concentration of Dextroamphetamine sulfate described in the method. Analyze the working solution initially then store one portion at ambient temperature and another portion in the refrigerator. Analyze these solutions against freshly prepared standards at the following intervals; 1 day, 7 days, 10 days, and 12 days (actual intervals may vary depending on laboratory workload or unforeseen events). Analyze the refrigerated samples only if the ambient samples fall out of the acceptance criteria and the ambient solution stability was unacceptably short.   1. Assay Sample Stability   Prepare three sample solutions using a a single preparation of a 1:1 mixture of the Amphetamine IR2:FC Pellets and Amphetamine DR:FC pellets with an equivalent dose of 30mg amphetamine mixed salts following the Assay preparation procedure in the method (spike placebos can be used). Analyze each working solution initially then store one portion at ambient temperature and another in the refrigerator (2-8C). Analyze these solutions against freshly prepared standards at the following intervals; 1 day, 7 days, 10 days and 15 days (actual intervals may vary depending on laboratory workload or unforeseen events). Analyze the refrigerated samples only if the ambient samples fall out of the acceptance criteria and the ambient solution stability was unacceptably short. | The solution will be considered stable if the substance exhibits 98.0 – 102.0% recovery of the amount of amphetamine placed into solution (initial time point).  If the recovery falls out of the specified range, the expiration date will be set to the day of the last passing result. |
| Robustness - Filter Study | The infinity time point solutions from the extraction efficiency study will be used in this experiment. At the filter step, an aliquot of each solution will be filtered using different types of filters and with centrifuging. The 0.45-m syringe filters used will contain the following materials PTFE and Nylon. The filtered solutions will be compared to a standard prepared by using the assay method standard preparation.  The filtered solutions will be compared to a centrifuged unfiltered sample using the % difference. The centrifuge will be set to an appropriate speed and time to make a clear supernatant. | Filtered sample vs. centrifuged sample:  % Difference: ±1.0% absolute  No extraneous peaks more than 0.2% are present in the filtered samples.  Any extraneous peak present in the filtered samples have a USP Resolution of NLT 1.5 from the API peak. |
| Robustness - 5 Factors / 8 Experiments Design of Experiments | The Robustness of the Assay methodology will be analyzed by a 5 Factor / 8 Experimental Design format described below:  Independent Variables   1. Amount in mL of Trifluoroacetic acid (TFA) in Mobile phase A 2. Column Temperature in °C 3. The pH of Mobile phase A 4. Detector wavelength 5. Mobile Phase Flow (mL/min)   Dependent Variable: % label claim of single preparation of a 1:1 mixture of the Amphetamine IR2:FC Pellets and Amphetamine DR:FC pellets with an equivalent dose of 30mg amphetamine mixed salts.  Design of Experiment   |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | | Exp # | TFA (mL) | Temp | pH MP A | Wavelength | Flow | | 1 | 9.5 | 42 | 2.0 | 254 | 0.8 | | 2 | 9.5 | 38 | 2.4 | 260 | 0.8 | | 3 | 10.5 | 42 | 2.4 | 254 | 0.8 | | 4 | 10.5 | 38 | 2.4 | 254 | 1.2 | | 5 | 9.5 | 42 | 2.0 | 254 | 1.2 | | 6 | 10.5 | 42 | 2.0 | 260 | 0.8 | | 7 | 9.5 | 38 | 2.4 | 260 | 1.2 | | 8 | 10.5 | 38 | 2.0 | 260 | 1.2 | | M | 10 | 40 | 2.2 | 257 | 1.0 | | Range | 10 ± 0.5 | 40 ± 2 | 2.2 ± 0.2 | 257 ± 3 | 1.0 ± 0.2 |   The result (% label claim) of each experiment will be used to determine the effect of changing each of the independent variables. The Effect will be calculated and ranked from lowest to highest in value. The M-values will be assigned using the following order: 1 (lowest) = -1.15, 2 = -0.49, 3 = 0, 4 = 0.49, and 5 (highest) = 1.15. The M-values will be used to normalize the effect responses and create a normalized scatter plot of the data to be analyzed.  The Effect will be plotted against the M-values and a regression line will be plotted. | The coefficient of determination (r2) of the regression line will be used to determine the robustness of the method.  r2: NLT 0.95  If the R2 is outside of the acceptance criteria, the parameter with the largest effect (deviation from zero) will be evaluated to determine the magnitude and controlled within the method, if necessary. The controls will be explained in the validation report and incorporated into the method. |

1. EXPERIMENTAL PARAMAETERS FOR CHIRAL ASSAY METHODOLOGY

The validation experimentation in this section will utilize the components of both the IR and DR pellets to represent the final product. The results for the experimentation will validate both types of pellets individually along with the mixture because the experimentation represents worse case regarding complexity of the matrix.

Experiments will be combined to increase laboratory efficiencies.

| **Chiral Parameter** | **Experimental Conditions** | **Acceptance Criteria** |
| --- | --- | --- |
| Accuracy | Prepare, in triplicate, solutions containing all excipients, at the proper formulation ratio, with Amphetamine sulfate spiked at 70, 100, and 130% of the nominal concentration of 0.3 mg/mL Dextroamphetamine as base.  The Average % recovery of the assayed value of each concentration will be used to determine the accuracy of the method.  Solution Theoretical Concentrations:  70% = 0.21 mg/mL Dextroamphetamine as base  100% = 0.3 mg/mL Dextroamphetamine as base  130% = 0.39 mg/mL Dextroamphetamine as base  Accuracy must be demonstrated in at least a ±30% window around the nominal concentration. If concentrations wider than the window demonstrate accuracy within the acceptance criteria, those results can be added to the Range of the method.  The concentrations do not have to match exactly but cannot cause the span of the Range to decrease significantly (NMT 3% absolute) from the planned range. | Mean percent recovery (n=3):  97.0 – 103.0% recovery of the average at each concentration  Individual preparations for the three working levels:  97.0%-103.0% from the theoretical concentration  Mean results are compared to the theoretical values for possible analytical bias. |
| Precision – Repeatability across the Range | Using the Accuracy preparations, determine the mean and %RSD of all of the % recoveries across the entire range. | The system will be considered precise across the analytical range if the RSD is NMT 1.5%. |
| Intermediate Precision | Both Analysts will complete the following on separate days and using separately made solutions:  Assay six separate preparations of a single preparation of a 1:1 mixture of the Amphetamine IR2:FC Pellets and Amphetamine DR:FC pellets with an equivalent dose of 30mg amphetamine mixed salts.  The %RSD of the six results, in percent assay (w/w), will be used to determine the sample repeatability. The Confidence Interval (=0.05) for the Sample Precision will be reported. | For each Analyst:  The methodology will be considered precise if the RSD of the six assay % Assay values is NMT 2.0%  The individual results must meet acceptance criteria of the product.  Comparison of Analyst A to B:  The difference between the two means (n=6) generated by the two analysts is ±2.5%. |
| Specificity – Placebo Interference | Generate representative HPLC chromatograms of a blank solution, an API solution, a sample solution, the working resolution solution and a placebo solution. The solutions will be injected in an unstressed condition.  Specificity will be determined using a HPLC equipped with a Diode Array Detector. The absence of significant excipient peaks at Dextroamphetamine and Levoamphetamine retention times in the placebo will be verified. The Peak Purity for Dextroamphetamine and Levoamphetamine in the sample solutions as calculated by the chromatographic software, using a Purity Threshold of 970, will be reported in the validation report. The separation of the Dextroamphetamine and Levoamphetamine will be determined by using the USP resolution.  If a peak is seen at the retention time of Dextroamphetamine and Levoamphetamine, the significance of the interference will be determined. | The methodology will be considered selective if any peaks generated from the placebo and blank solution are not within ±0.2 minutes of the main peaks or if there is a peak at the retention time of the main peaks are not considered significant (NMT 0.2% of a standard at the nominal concentration).  The USP Resolution between the Dextroamphetamine and Levoamphetamine peaks will be NLT 1.5.  If the peak purity falls below 970, the chromatography will be investigated, and the results of the investigation will be placed into the validation report. These peaks will be listed in the validation report. |
| Linearity | Prepare solutions over a range of concentrations encompassing the analytical sample concentration (0.15mg/mL to 0.45mg/mL).  Three stock solutions should be made and five dilutions from each stock solution with concentrations: 0.15mg/mL, 0.21mg/mL, 0.3mg/mL, 0.39g/mL, and 0.45mg/mL of Dextroamphetamine as base.  Determine the response of Dextroamphetamine using the HPLC system described in the methodology.  The linear X & Y (Concentration & Peak Area) data is normalized (divide each level’s data by the related 100% data value) and perform a linear regression analysis of the results versus concentration. The linear regression analysis will also be calculated for the original data including coefficient of determination (r2) and Residual Sum of Squares. | Normalized Data  Slope of the regression line: 1.0 ± 0.1  Y-intercept within ±3.0% from zero  Original Data  r2: NLT 0.999  Area response of the y-intercept NMT 2.0% of the response of the 100% nominal concentration value.  Report the Residual sum of squares |
| Range | The concentration range over which the assay is shown to be linear, accurate and precise. | Report the range of concentrations where the method is linear, accurate and precise. |
| Robustness - Solution Stability | Standard Stability  Prepare a standard solution at the nominal concentration of Dextroamphetamine described in the method. Analyze the working solution initially then store one portion at ambient temperature and another portion in the refrigerator. Analyze these solutions against freshly prepared standards at the following intervals: 1 day, 7 days, 10 days, and 12 days (actual intervals may vary depending on laboratory workload or unforeseen events). Analyze the refrigerated samples only if the ambient samples fall out of the acceptance criteria and the ambient solution stability was unacceptably short.  Assay Sample Stability  Prepare a sample solution using a a single preparation of a 1:1 mixture of the Amphetamine IR2:FC Pellets and Amphetamine DR:FC pellets with an equivalent dose of 30mg amphetamine mixed salts. following the Assay preparation procedure in the method (spike placebos can be used). Analyze each working solution initially then store one portion at ambient temperature and another in the refrigerator (2-8C). Analyze these solutions against freshly prepared standards at the following intervals: 1 day, 7 days, 10 days and 15 days (actual intervals may vary depending on laboratory workload or unforeseen events). Analyze the refrigerated samples only if the ambient samples fall out of the acceptance criteria and the ambient solution stability was unacceptably short. | The solution will be considered stable if the substance exhibits 98.0 – 102.0% recovery of the amount of Dextroamphetamine as base placed into solution (initial time point).  If the recovery falls out of the specified range, the expiration date will be set to the day of the last passing result. |
| Robustness - Filter Study | The infinity time point solutions from the extraction efficiency study will be used in this experiment. At the filter step, an aliquot of each solution will be filtered using different types of filters and with centrifuging. The 0.45-m syringe filters used will contain the following materials PTFE and Nylon. The filtered solutions will be compared to a standard prepared by using the assay method standard preparation.  The filtered solutions will be compared to a centrifuged unfiltered sample using the % difference. The centrifuge will be set to an appropriate speed and time to make a clear supernatant. | Filtered sample vs. centrifuged sample:  % Difference: ±1.0% absolute  No extraneous peaks more than 0.2% are present in the filtered samples. Any extraneous peak present in the filtered samples have a USP Resolution of NLT 1.5 from the API peak. |
| Robustness - 5 Factors / 8 Experiments Design of Experiments | The Robustness of the Chiral Assay methodology will be analyzed by a 5 Factor / 8 Experimental Design format described below:  Independent Variables   1. Amount of MeOH in Mobile phase 2. Column Temperature in °C 3. The pH of Mobile phase 4. Detector wavelength 5. Column   Dependent Variable: % assay (DEX) of single preparation of a 1:1 mixture of the Amphetamine IR2:FC Pellets and Amphetamine DR:FC pellets with an equivalent dose of 30mg amphetamine mixed salts.  Design of Experiment   |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | | Exp # | MeOH | Temp | pH MP | Wavelength | Column | | 1 | 8 | 28 | 1.4 | 207 | 1 | | 2 | 8 | 22 | 1.6 | 213 | 1 | | 3 | 12 | 28 | 1.6 | 207 | 1 | | 4 | 12 | 22 | 1.6 | 207 | 2 | | 5 | 8 | 28 | 1.4 | 207 | 2 | | 6 | 12 | 28 | 1.4 | 213 | 1 | | 7 | 8 | 22 | 1.6 | 213 | 2 | | 8 | 12 | 22 | 1.4 | 213 | 2 | | M | 10 | 25 | 1.5 | 210 | N/A | | Range | 10 ± 2 | 25 ± 3 | 1.5 ± 0.1 | 210 ± 3 | 1 or 2 |   The result (% assay of DEX) of each experiment will be used to determine the effect of changing each of the independent variables. The Effect will be calculated and ranked from lowest to highest in value. The M-values will be assigned using the following order: 1 (lowest) = -1.15, 2 = -0.49, 3 = 0, 4 = 0.49, and 5 (highest) = 1.15. The M-values will be used to normalize the effect responses and create a normalized scatter plot of the data to be analyzed.  The Effect will be plotted against the M-values and a regression line will be plotted. | The coefficient of determination (r2) of the regression line will be used to determine the robustness of the method.  r2: NLT 0.95  If the R2 is outside of the acceptance criteria, the parameter with the largest effect (deviation from zero) will be evaluated to determine the magnitude and controlled within the method, if necessary. The controls will be explained in the validation report and incorporated into the method. |

1. EXPERIMENTAL PARAMETERS FOR DISSOLUTION METHODOLOGY

Experiments will be combined to increase laboratory efficiencies.

| **Dissolution Parameter** | **Experimental Conditions** | **Acceptance Criteria** |
| --- | --- | --- |
| Intermediate Precision | Both Analysts will complete the following on separate days and using separately made solutions:  5-mg strength  Analyze twelve separate dissolution vessels six separate preparations of a single preparation of a 1:1 mixture of the Amphetamine IR2:FC Pellets and Amphetamine DR:FC pellets with an equivalent dose of 5mg amphetamine mixed salts. The samples will be prepared by following the method listed including the time points listed in the method.  30-mg strength  Analyze twelve separate dissolution vessels six separate preparations of a single preparation of a 1:1 mixture of the Amphetamine IR2:FC Pellets and Amphetamine DR:FC pellets with an equivalent dose of 30mg amphetamine mixed salts. The samples will be prepared by following the method listed including the time points listed in the method.  The %RSD of the twelve results from the 60-minutes time point, in percent release, will be used to determine the sample repeatability. The confidence interval (=0.05) for the sample precision will be reported at each of the sample time points. | Each Analyst:  The methodology will be considered precise if the RSD of the twelve % release values is NMT 5.0%.  The individual results will meet the acceptance criteria for the product.  Comparison of Analyst A to Analyst B  The two profiles will be compared using F2 calculations. The F2 value must be greater than 50. |
| Robustness – Solution Stability | 1. Standard Solution Stability   Prepare a working standard solution to the nominal concentration of Dextroamphetamine described in the methodology. Analyze the working standard solution initially then store one portion at ambient temperature. Analyze these standard solutions against freshly prepared standards at the following intervals; 1 day, 7 days, 10 days, and 14 days (actual intervals may vary depending on laboratory workload or unforeseen events).     1. Dissolution Sample Solution Stability   Prepare three sample solutions following the Dissolution preparation procedure in the method for the5-mg strength. Analyze each working sample solution initially then store at ambient temperature. Analyze these sample solutions against freshly prepared standards at the following intervals; 24 hours, 2 day, 3 days and 5 days (actual intervals may vary depending on laboratory workload or unforeseen events). | Standard solution  The solution will be considered stable if the substance exhibits 98.0 – 102.0% recovery  Sample solution  97.0 – 103.0% recovery of the amount of Amphetamine placed into solution (initial time point).  If the recovery falls out of the specified range, the expiration date will be set to the day of the last passing result. |
| Robustness - Filter Study | A single lot of 30-mg strength will be used to determine the effect of filtration used in the dissolution sample preparation. The 5-hour time point solutions will be used in this experiment. At the filter step, an aliquot of each solution will be filtered using different types of filters. The filters used will be 10-m and 35-mm (UHMW PE) filters, if available. The % release for each filtered and a centrifuged unfiltered sample will be calculated. The filtered solutions will be compared to the unfiltered (centrifuged) results to determine the impact of filter pore size on the dissolution method. | Filtered sample vs. centrifuged sample  % Difference: NMT 2% absolute |
| Robustness - 5 Factors / 8 Experiments Design of Experiments | The Robustness of the Dissolution methodology will be analyzed by a 5 Factor / 8 Experimental Design format described below:  Independent Variables   1. Basket Speed 2. Bath Temp 3. Basket Height 4. Dissolution Instrument (DISS) 5. Media Volume   Dependent Variable: % release of single preparation of a 1:1 mixture of the Amphetamine IR2:FC Pellets and Amphetamine DR:FC pellets with an equivalent dose of 30mg amphetamine mixed salts at 2-hour (Acid phase) and 5-hour time points  Design of Experiment   |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | | Exp # | Paddle Speed | Bath Temp | Paddle Ht | DISS | Volume | | 1 | 47 | 38 | 25 | 1 | 735 / 930 | | 2 | 47 | 36 | 30 | 2 | 735 / 930 | | 3 | 53 | 38 | 30 | 1 | 735 / 930 | | 4 | 53 | 36 | 30 | 1 | 765 / 970 | | 5 | 47 | 38 | 25 | 1 | 765 / 970 | | 6 | 53 | 38 | 25 | 2 | 735 / 930 | | 7 | 47 | 36 | 30 | 2 | 765 / 970 | | 8 | 53 | 36 | 25 | 2 | 765 / 970 | | M | 50 | 37 | 25 | 1 | 750 / 950 | | Range | 50 ± 3 | 37 ± 1 | 25 ± 5 | 1 or 2 | 750 ± 15  950 ± 20 |   The result (% release) of each experiment will be used to determine the effect of changing each of the independent variables. The Effect will be calculated and ranked from lowest to highest in value. The M-values will be assigned using the following order: 1 (lowest) = -1.15, 2 = -0.49, 3 = 0, 4 = 0.49, and 5 (highest) = 1.15. The M-values will be used to normalize the effect responses and create a normalized scatter plot of the data to be analyzed.  The Effect will be plotted against the M-values and a regression line will be plotted. | The Design of Experiments will be completed twice, once for the 0.01N HCl apparatus and then for the pH 6.8 buffer apparatus.  The coefficient of determination (R2) of the regression line will be used to determine the robustness of the method.  R2: NLT 0.95  If the R2 is outside of the acceptance criteria, the parameter with the largest effect (deviation from zero) evaluated to determine the magnitude and controlled within the method, if necessary. The controls will be explained in the validation report and incorporated into the method. |

1. EXPERIMENTAL PARAMETERS FOR DEGRADATION PRODUCT ANALYSIS

Experiments will be combined to increase laboratory efficiencies. See section 8.0 for the names, relative retention times, and relative response factors.

| **Impurities Parameter** | **Experimental Conditions** | **Acceptance Criteria** |
| --- | --- | --- |
| Accuracy | For degradation products ID #2, 3, 4, benzaldehyde, 5, and 6:  Prepare three (3) spiked placebo solutions at each of the concentrations specified below:  1.2 µg/mL: Limit of Quantitation (0.08% as base; 0.05% as salts)  12 µg/mL: 100% of limit (0.8% as base; 0.5% of salts)  18 µg/mL: 150% of limit (1.2% as base; 0.75% as salts)  Assay each solution as described in the impurities test procedure. | |  |  | | --- | --- | | Impurity Level (%) | % Difference  (from theoretical amount) | | ≤ 0.10 | ± 0.03% absolute | | ≤ 0.50 | ± 0.06% absolute | |
| Precision – Repeatability across the Range | Using the Accuracy preparations, determine the mean and %RSD of all of the % recoveries across the entire range. | The system will be considered precise across the analytical range if the RSD is NMT 10%. |
| Intermediate Precision | Both Analysts will complete the following on separate days and using separately made solutions:  Prepare six (6) placebo solutions spiked with the known impurities at the acceptance criteria of 0.5% (12 µg/mL). The samples will be analyzed, and the results will be recorded. The confidence interval (a=0.05) for each data set will be calculated. | Each Analyst:  The methodology will be considered precise, if the RSD of the six spiked placebo preparations for each of the specified degradation products is NMT 10.0%.  Comparison of Analysts A & B:   |  |  | | --- | --- | | Impurity Level (%) | % Difference  (Between Two Analysts) | | ≤ 0.10 | ± 0.05 absolute | | ≤ 0.50 | ± 0.15 absolute | |

| **Impurities Parameter** | **Experimental Conditions** | **Acceptance Criteria** |
| --- | --- | --- |
| Specificity – Degradation Experimentation & Placebo Interference | Resolution Chromatogram  Create the resolution solution that will contain all of the known degradation products at 12mg/mL and dextroamphetamine sulfate at 1.5mg/mL as base and inject the solution onto the Impurities system specified in the methodology.  Placebo Interference  The absence of significant excipient peaks at Amphetamine retention time in the placebo will be verified. The peak purity for the Amphetamine in the sample solutions as calculated by the chromatographic software, using a Purity Threshold of 970, will be reported in the validation report. | No significant (≤0.2%) interference of the primary analytes’ responses.  The USP Resolution between Amphetamine and the known impurity peaks ≥ 1.5.  If the peak purity falls below 970, the chromatography will be investigated and the results of the investigation will be placed into the validation report. These peaks will be listed in the validation report. |
| Linearity | Prepare solutions over a range of concentrations encompassing the analytical sample concentration (1.2mg/mL to 18 mg/mL).  Three stock solutions should be made and five dilutions from each stock solution with concentrations: 1.2mg/mL, 2.4mg/mL, 6.0mg/mL, 12mg/mL, and 18mg/mL of each known impurities.  Determine the response of each degradation product using the HPLC system described in the methodology. The linear regression analysis will also be calculated for the original data including coefficient of determination (r2) and Residual Sum of Squares. | r2: NLT 0.99  Report the Residual Sum of Squares |
| Range | The concentration range over which the method is shown to be linear, accurate and precise. | Report the range of concentrations where the method is linear, accurate and precise. |
| Quantitation and Detection Limit | Quantitation Limit (QL)  A solution prepared with the impurities listed in section 8.0 at 1.2µg/mL (0.05% as salt) will be injected 6 times.  Detection Limit (DL)  A solution prepared with the impurities listed in section 8.0 at 0.7µg/mL (0.03% as salt) will be injected 3 times. | The QL will be the concentration determined by the Quantitation Limit calculation, Signal-to-Noise ratio NLT 10:1 and an RSD of NMT 10%.  For DL: The peaks of interest will be present in three DL injections and will be reported in the validation report. S/N will be greater than 3:1 in all three injections. |
| Robustness – Solution Stability | Prepare three spiked sample solutions (12 µg/mL spiked placebos can be used) following the preparation procedure in the method. Analyze each working solution initially then store one portion at ambient temperature and another in the refrigerator at 2-8C. Analyze these solutions against freshly prepared standards at intervals specified below (actual intervals may vary depending on laboratory workload). Solution stability for impurities will be calculated on % impurity levels. Analyze the refrigerated samples only if the ambient samples fall out of the acceptance criteria and the ambient solution stability was unacceptably short.  Sample: Initial, 1 day, 2 days, 3 days | Sample: ± 0.15% absolute of initial |
| Robustness – Filter Study | The 12 µg/mL spiked placebos will be used to determine the effect of filtration used in the impurities sample preparation. In the filter step, an aliquot of each solution will be filtered using different types of filters and with centrifuging. The 0.45-m syringe filters used will contain the following materials PTFE and Nylon. The filtered solutions will be compared to a standard at 12 µg/mL prepared by using the assay method standard preparation.  The results of the filtered solutions will be compared to the results of a centrifuged unfiltered sample using the % difference. The centrifuge will be set to an appropriate speed and time to make a clear supernatant. | Filtered sample vs. centrifuged sample  % Difference: ±0.05% absolute |
| Robustness - 5 Factors / 8 Experiments Design of Experiments | The Robustness of the Assay methodology will be analyzed by a 5 Factor / 8 Experimental Design format described below:  Independent Variables   1. Amount in mL of Trifluoroacetic acid (TFA) in Mobile phase A 2. Column Temperature in °C 3. The pH of Mobile phase A 4. Detector wavelength 5. Mobile Phase Flow (mL/min)   Dependent Variable: % label claim of single preparation of a 1:1 mixture of the Amphetamine IR2:FC Pellets and Amphetamine DR:FC pellets with an equivalent dose of 30mg amphetamine mixed salts.  Design of Experiment   |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | | Exp # | TFA (mL) | Temp | pH MP A | Wavelength | Flow | | 1 | 9.5 | 42 | 2.0 | 254 | 0.8 | | 2 | 9.5 | 38 | 2.4 | 260 | 0.8 | | 3 | 10.5 | 42 | 2.4 | 254 | 0.8 | | 4 | 10.5 | 38 | 2.4 | 254 | 1.2 | | 5 | 9.5 | 42 | 2.0 | 254 | 1.2 | | 6 | 10.5 | 42 | 2.0 | 260 | 0.8 | | 7 | 9.5 | 38 | 2.4 | 260 | 1.2 | | 8 | 10.5 | 38 | 2.0 | 260 | 1.2 | | M | 10 | 40 | 2.2 | 257 | 1.0 | | Range | 10 ± 0.5 | 40 ± 2 | 2.2 ± 0.2 | 257 ± 3 | 1.0 ± 0.2 |   The result (% label claim) of each experiment will be used to determine the effect of changing each of the independent variables. The Effect will be calculated and ranked from lowest to highest in value. The M-values will be assigned using the following order: 1 (lowest) = -1.15, 2 = -0.49, 3 = 0, 4 = 0.49, and 5 (highest) = 1.15. The M-values will be used to normalize the effect responses and create a normalized scatter plot of the data to be analyzed.  The Effect will be plotted against the M-values and a regression line will be plotted. | The coefficient of determination (r2) of the regression line will be used to determine the robustness of the method.  r2: NLT 0.95  If the r2 is outside of the acceptance criteria, the parameter with the largest effect (deviation from zero) evaluated to determine the magnitude and controlled within the method, if necessary. The controls will be explained in the validation report and incorporated into the method. |

1. EXPERIMENTAL PARAMETERS FOR MOISTURE ANALYSIS BY KARL FISCHER TITRATION

Experiments will be combined to increase laboratory efficiencies.

| **Water Parameter** | **Experimental Conditions** | **Acceptance Criteria** |
| --- | --- | --- |
| Intermediate Precision | Both Analysts will complete the following on separate days:  Assay six separate preparations of a single lot of Coated Granules The samples will be prepared by following the Moisture determination preparation procedure.  The %RSD of the six results, in percent water, will be used to determine the sample repeatability. The Confidence Interval (=0.05) for the Sample Precision will be reported. | For each Analyst:  The methodology will be considered precise if the RSD of the six percent water values is NMT 10.0%  The individual results must meet acceptance criteria of the product.  Comparison of Analysts A & B:  The difference between the result means is ±2.0% absolute. |
| Robustness - Extraction Efficiency | A single batch of coated granules will be analyzed by extracting the moisture from the matrices at 1 minute, 2 minutes and 3 minutes. All of the results will be compared to the acceptance criteria listed in this protocol. | The absolute difference between each of the bracketing times and the desired stir time (2 minutes) is less than ± 0.5. |

1. EXPERIMENTAL PARAMETERS FOR PARTICLE SIZE DISTRIBUTION BY LIGHT DIFFRACTION

Experiments will be combined to increase laboratory efficiencies.

| **PSD Parameter** | **Experimental Conditions** | **Acceptance Criteria** |
| --- | --- | --- |
| Method Development | During the development of the methodology the following parameters were examined:  Refractive Index (RI)  Absorbance Index (AI)  Obscuration  Sample Dispersion study | Report the parameters and list in the methodology. |
| Intermediate Precision | Both Analysts will complete the following on separate days:  Analyze the same lot of DR pellets (n=6) using the set parameters above. The means in microns of the D10, D50, and D90 generated. The %RSD of the measurements will be generated for the results (n=6).  The Confidence Interval (=0.05) for the Sample Precision will be reported.  The %RSD of the measurements will be generated for the results (n=12). | For each Analyst:  Report the %RSD (n=6) for D10, D50, and D90 results.  D10: NMT 15 %RSD  D50: NMT 10 %RSD  D90: NMT 15 %RSD  Comparison of Analysts A & B:  The difference between analysts in the mean for D10, D50, and D90 results will be reported. Report the %RSD (n=12) for D10, D50, and D90 results.  D10: NMT 15 %RSD  D50: NMT 10 %RSD  D90: NMT 15 %RSD |
| Microscopic Examination | Take micrographs with an optical microscope and measure the size of some of the particles. Compare the size of the particles from the micrographs and the Particle size distribution by light diffraction results. | Report and discuss the results of the comparison. |

1. EXPERIMENTAL PARAMETERS FOR IDENTIFICATION METHODOLOGY

Experiments will be combined to increase laboratory efficiencies.

| **ID Parameter** | **Experimental Conditions** | **Acceptance Criteria** |
| --- | --- | --- |
| Specificity - Interference | 1. Identification – Retention Time Comparison   Generate representative HPLC chromatograms of standard solution. Specificity will be determined using a HPLC equipped with a Photodiode Array Detector. The Peak Purity calculated by the chromatographic software will be used to determine the Specificity of Amphetamine in the identification method.  A sample and a standard will be injected on a system setup in accordance with the Identification method (Retention Time) stated in the method. The Retention Times (RT) will be recorded and compared by calculating the ratio between the RT of the API peak in the sample over the RT of the API peak of the standard.   1. Identification – UV Spectra   Using the injections listed above, spectra of the standard and sample amphetamine peak will be compared. The maxima and minima generated by the standard and sample injections. | 1. The methodology will be considered selective if the peak purity is above 970. If the peak purity falls below 970, the chromatography will be investigated and the results of the investigation will be placed into the validation report.   The ratio of Amphetamine RT of sample over RT of standard should be 98.0 – 102.0%.   1. The standard and sample maxima and minima must be ±2nm |
| Intermediate Precision | A second analyst will repeat the Specificity experiments above. | Both analysts must meet the acceptance criteria listed above. |

1. STATISICAL ANALYSIS
   1. Percent Recovery

The % Recovery will be determined for each sample separately using the following equation:



Where:



* 1. Confidence Interval

The Confidence Interval (CI) for a set of data will be determined using the following equation:



Where:





* 1. Relative Standard Deviation

The Relative Standard Deviation (RSD) of the replicates will be determined using the following equation:



Where:



X = Result Value

\_

X = Average of n results

* 1. Percent Significance

The % significance of interference (SIG) will be determined using the following equation:



C = Standard Concentration (mg/mL)

Ap = Area of Interfering peak

As = Area of Standard

V = Sample volume (mL)

Ws = Sample weight (mg)

* 1. Percent Change (% Difference)

The % Change between two results will be determined by using the following equation:



A = Comparator Result

B = Sample Result

* 1. Effect Factor for Robustness

The Effect will be calculated using the following equation:







* 1. Percent Change (% Difference)

The % Change between two results will be determined by using the following equation:



A = Result A

B = Result B

* 1. Two One-side Test (TOST)

The Upper and Lower Confidence interval will be generated using the following equation:



CI = Confidence Interval

1 = Average of results from method #1

2 = Average of results from method #2

𝑡 0.1(𝑛1+𝑛2−2) = 𝑡 𝑣𝑎𝑙𝑢𝑒 𝑤𝑖𝑡ℎ 𝛼 = 0.1 𝑎𝑛𝑑 𝑑𝑓 = 𝑛1 + 𝑛2 − 2

Sp = Pooled Standard Deviation

n1 = Size of data sampling from method #1

n2 = Size of data sampling from method #2

1. GLOSSARY OF TERMS
   1. Specificity

**Definition:** The specificity of a test method is its ability to assess the analyte in the presence of compounds, which may be expected to be present in the sample matrix. Typically, these might include impurities and degradants.1

* 1. Solution Stability

**Definition:** The solution stability will be defined, as the storage conditions and the amount of time that a solution containing the analyte can be stored and the results from the analysis is still valid.

* 1. Limit of Quantitation (QL)

**Definition:** The ICH guidelines express the QL as the lowest amount of analyte in a sample, which can be quantitatively determined with suitable precision and accuracy.1

* 1. Limit of Detection (DL)

**Definition:** The ICH Guidelines express the DL as the lowest amount of analyte in a sample, which can be detected but not necessarily quantitative as an exact value.1

* 1. Accuracy

**Definition:** Accuracy of a test method is defined by ICH as an expression of the closeness of agreement between the measured value and the value, which is accepted either as a conventional true value or an accepted reference value.1

* 1. Precision

**Definition:** The ICH defines the precision of an analytical procedure as the closeness of agreement between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions.1

* + 1. System and Method Repeatability

**Definition:** Repeatability is defined by ICH as precision under the same operating conditions over a short interval.1

* + 1. Intermediate Precision

**Definition:** Intermediate Precision is expressed in the ICH guidelines as the within-laboratory variations: different days, different analysts, different equipment, etc…1

* 1. Linearity

**Definition:** The linearity of an analytical procedure is defined as its ability to obtain test results, which are directly proportional to the concentration of the analyte in the sample within a given range.1 Linearity is typically evaluated by linear regression of a plot of signals as a function of analyte concentration.

* 1. Range

**Definition:** The range of an analytical procedure is the interval between the upper and lower concentrations (amounts) of analyte in the sample (including these concentrations) for which it has been demonstrated that the method has a suitable level of precision, accuracy and linearity.1

* 1. Identification Methodology

**Definition:** According to the ICH guidelines, a suitable identification test should be able to discriminate between compounds of closely related structures which are likely to be present in the sample matrix.2

1. REFERENCES
   1. ICH Q2(R1), “Validation of Analytical Procedures: Text and Methodology”
   2. ICH Q3B(R2), “Impurities in New Drug Products”
   3. FDA Guidance for Industry on “Analytical Procedures and MethodsValidation for Drugs and Biologics”, February 2014.
   4. Current revision of SOP-00026, “Validation of Analytical Procedures”
   5. USP General Chapter <621>, “Chromatography”
   6. USP General Chapter <1092>, “The Dissolution Procedure: Development and Validation”
   7. Recipharm Report #RT DF153-03 version 01, “DF153: Technical Development Report of HPLC Assay and Related Compound Method based on USP Method”
   8. Recipharm Report #VA 017 version 01, “Validation Report for the Dissolution Method of Amphetamine Salts in Accordance with MTH 1022”
   9. Recipharm Report #VA 046 version 01, “Validation Report for the Assay and Degradation Product Method of Amphetamine Formulations in Accordance with MTH 1058”
   10. Recipharm Report #VA 061 version 01, “Validation Report Addendum for the Amphetamine Degradation Product Response Factors Determination in Amphetamine Formulation in Accordance with MTH 1058”
   11. Recipharm Report #RT DF153-04 version 01, “DF153: Stressed Degradation Study Report”

ATTACHMENT #1: DRAFT METHODOLOGY FOR VALIDATION