



## USP Guideline on Procedures for Mechanical Calibration and Performance Verification Test Apparatus 1 and Apparatus 2

### Scope:

This document provides a description of best practices associated with the mechanical calibration and performance verification test for the USP basket and paddle dissolution apparatus and test assembly. The best practices described herein have been developed based on experience gained by the USP laboratory and with suggestions from the USP General Chapters Dosage Forms Expert Committee; Subcommittee A on Performance Verification Testing (2015-2020 cycle). These best practices are intended to provide an improved operating range and process capability for the dissolution test by focusing on critical apparatus and test parameters. Except where this document specifically refers to compendial requirements in the USP-NF, the information in this document is not binding and is intended to aid the dissolution laboratory in the effort to obtain valid dissolution testing results by ensuring that the assembly is operating well within the intended operating ranges of the apparatus/test.

In some cases, the recommendations given herein are more stringent and more comprehensive than information found in USP General Chapter <711> *Dissolution*. These recommendations are provided as best practices and are not intended to supersede the content of <711>. General Chapter <711> *Dissolution* is official USP text and subject to harmonization agreements.

### Audience:

Scientists, technicians, and lab managers with practical experience of dissolution testing who employ the performance verification test.

### Disclaimer:

Certain commercial equipment, instruments, vendors, or materials may be recognizable in figures contained in the following guidelines. Such identification of a brand or product does not imply approval, endorsement, or certification by USP, nor does it imply that the equipment, instrument, vendor, or material is necessarily the best available for the purpose or that any other brand or product was judged to be unsatisfactory or inadequate.

This version of the document represents a continuing effort to provide detailed information describing the procedures that, if used, will ensure a properly qualified dissolution test assembly. As new information relevant to that goal becomes available, this document may be revised.



## I. Introduction

Analytical instrumental qualification (AIQ), which includes design qualification (DQ), installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ), is widely accepted. USP General Chapter <1058> *Analytical Instrument Qualification* describes AIQ in detail. [Note—All USP general chapters numbered above 1000 are for informational purposes only. See *General Notices and Requirements* for further clarification]. For dissolution assemblies, the mechanical calibration steps in this guide should satisfy OQ and parts of IQ. PQ may be satisfied by a performance verification test (PVT), in support of which USP makes available official USP Dissolution Performance Verification Standard – Prednisone RS for use in qualifying Apparatus 1 (basket) and Apparatus 2 (paddle).

## II. Definitions

**Apparatus:** The basic unit for the in-vitro performance testing of dosage units. The apparatus consists of a container (vessel) for the dosage unit and dissolution medium, a device for promoting agitation of the dissolution medium (stirring element), temperature control and support to hold the vessel and stirring element in a fixed orientation. Typically, six to eight apparatus are grouped into a dissolution test assembly.

**Stirring Element:** A paddle, rotating basket, and/or shaft combination used to promote the movement of the dissolution medium relative to the dosage unit under test.

**Position:** Location within a dissolution test assembly where a particular apparatus is employed.

**Assembly:** A combination of multiple apparatus that provides temperature control, control of stirring elements, and provides the opportunity for simultaneous or individual (i.e., staggered) start of the apparatus.

**Vessel Support Plate (Base plate):** The structural element of the test assembly that fixes and provides support for the vessels during testing. Some assembly designs use the drive unit plate to position the vessels.

**Dissolution Drive Head Unit:** Support structure for the drive mechanism and for stirring elements. The moving parts of the drive unit are protected from contamination by a cover that also provides protection against injury to the operator. In some configurations the drive head unit can also be positioned to prevent evaporative loss of media.

**Dissolution System:** Test assembly connected to sampling and filter unit but without instrumentation such as UV/VIS spectrophotometer or HPLC chromatograph.

**Run:** Common terminology for an individual dissolution experiment. As given under *Interpretation* in <711> *Dissolution* the smallest sample set tested is comprised of six



dosage units. A run may include multiple sampling intervals but is concluded by the withdrawal of the sample aliquots (with filtration) at the final specified time point.

### III. Mechanical Calibration

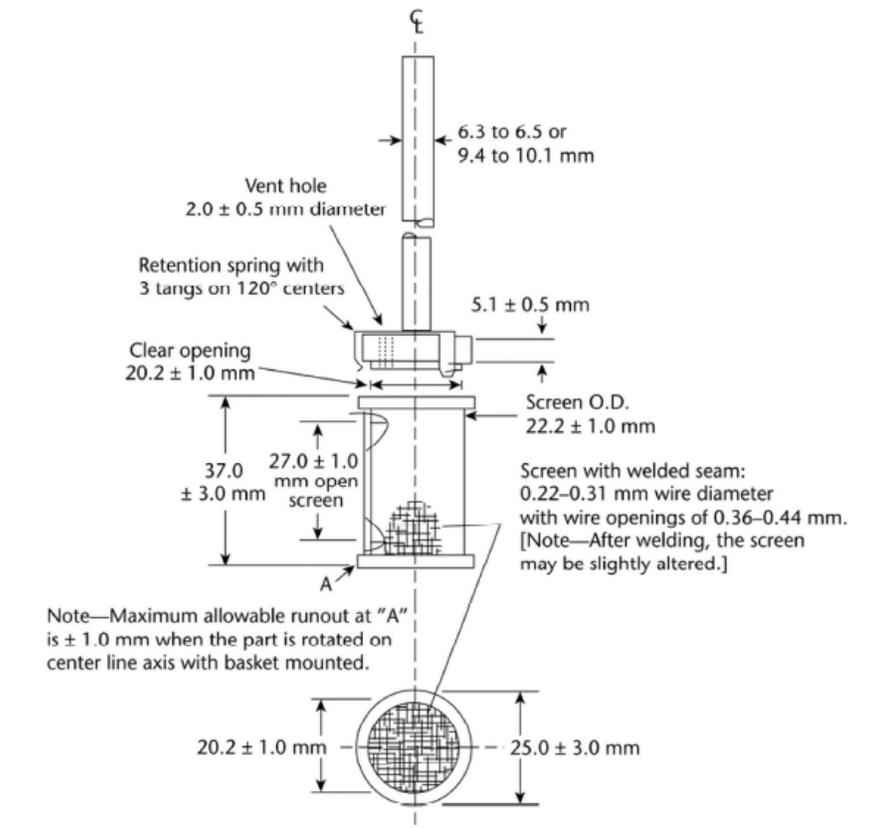
A. *Environment* – Bench tops are used to support dissolution equipment. A suitable bench top must be level, sturdy and provide a high inertial mass to limit vibration. Disturbances such as the placement of large volume solution containers may produce transient vibration but should not affect the levelness of the surface. The presence of sonication equipment, HPLC equipment, shakers, and other equipment that may produce vibration should be avoided.

B. *Bench top levelness* – A digital or spirit level should be used to measure the inclination of the bench top in two orthogonal directions. Bench top surface inclination should be NMT 1°. The influence of bench top surface inclination on the dissolution assembly is compensated by leveling devices (see Component Conformance, Vessel Support Base below).

C. *Assembly* – All vessels and individual parts of the stirring elements (shafts, baskets, paddles, or paddle blades) should be uniquely identified, documented, and kept in the same position and in the same test assembly for all dissolution runs. For ease of identification and record keeping, apparatus positions of the vessel support plate of the dissolution test assembly should be identified systematically.

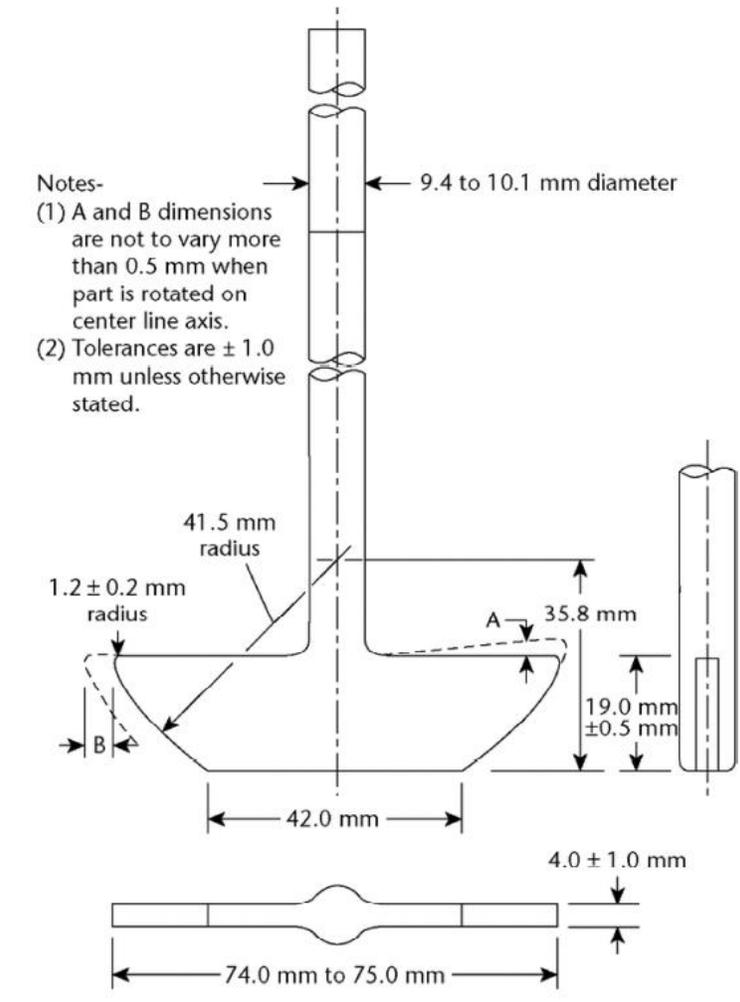
D. *Component Conformance*

1. ***Basket (Apparatus 1)*** – Basket dimensions must conform to Figure 1: Basket Stirring Element. Use a micrometer and/or a Vernier caliper to measure dimensional requirements. The basket mesh cylinder should be at right angles to the plane of the bottom and top rings. Use a machinist square, feeler gauge or gauge block, and Vernier caliper to determine deviation (e.g., 0.5 mm deviation over 37 mm height is about 1 degree). The mesh has no gross defects or buildup of residue from media or other formulation components.



**Figure 1. Basket Stirring Element**

2. **Paddle (Apparatus 2)** – Paddle dimensions must conform to Figure 2: Paddle Stirring Element. Use a micrometer and/or Vernier caliper. The condition of the surfaces of the paddle blade and shaft should be free of gross defects including scratches, and if coated, the coated surfaces are also free of gross scratches, peeling or pitting and are otherwise intact.



**Figure 2: Paddle Stirring Element**

3. **Vessel** –The vessel is cylindrical, with a hemispherical bottom and with one of the following dimensions and capacities: for a nominal capacity of 1 L, the height is 160–210 mm, and its inside diameter is 98–106 mm; for a nominal capacity of 2 L, the height is 280–300 mm, and its inside diameter is 98–106 mm; and for a nominal capacity of 4 L, the height is 280–300 mm, and its inside diameter is 145–155 mm. Its sides are flanged at the top. A fitted cover may be used to retard media evaporation. Documentation is available from vendors that may provide vessel dimensional measurements. For measuring the dimensions directly, use a vernier caliper or depth gauge. Studies show that different dimensions especially inner diameter may produce different dissolution rates, even though those dimensions are within the tolerances for vessels. It is suggested that vessels of very similar dimensions be used within a

run to reduce variability. The vessel inner surfaces are clean, without visible etching or scratches.

E. *Alignments*

1. **Vessel Support Plate (Base plate)** – Base plate inclination is not more than  $0.5^\circ$  in each of two orthogonal directions (typically measured from side-to-side and front-to back; see Figure 3). Most base plate designs allow adjustment of levelness, if necessary, usually by rotating adjusting screws on the feet of the support and frame assembly. The strain of the test assembly structure from the mass of the filled water bath should also be considered by confirming the levelness of the vessel support plate with the water bath filled. The condition of the vessel support plate should be visually evaluated and found to be uniform, even, and not distorted or misshapen. The vessel support plate should resist deformation when under load by filled vessels.



Figure 3. Measurement of vessel support plate levelness using electronic protractor.

2. **Shaft verticality** – Use an electronic protractor to check the verticality of the stirring elements. Measure the verticality for each stirring element in two orthogonal positions (see Figure 4). The ideal reading obtained on a vertical surface is  $90.0^\circ$ . The deviation should be no more than  $0.5^\circ$  from  $90.0^\circ$  for this measurement.



Figure 4. Measurement of shaft verticality using electronic protractor.

3. **Vessel verticality** – Use an electronic protractor to measure the verticality of each vessel in the dissolution assembly. Check the verticality for each vessel in two positions oriented at 90° around the vessel axis. The measurements are made on the vessel inner surface. The ideal reading obtained on a vertical surface is 90.0°. The deviation should be no more than 0.5° from 90.0° for this measurement.

4. **Centering** – Determine the centering of the stirring element shaft within the vessel for each position. Centering can be evaluated for the stirring element placed within the vessel as it would be during the test. Measure the centering with respect to the cylindrical vessel in two locations. The upper measurement is taken not more than 2 cm below the vessel flange. The lower measurement is taken at the same approximate height from the bottom surface of the vessel which corresponds to the 500mL fill level in the vessel (see Figure 5). Use the centering gauge to evaluate the alignment of the stirring element and the vessel. The difference between the largest and smallest observed readings should not be greater than 2.0 mm for 360° rotation.



Figure 5. Using a centering gauge to determine the deviation of the vessel central axis from that of the stirring element at approximately the 500mL fill level.

5. **Basket Wobble** – Use a dial test indicator to measure the wobble of each of the basket stirring elements with the dial test indicator probe tip at the bottom basket rim (See Figure 6). Perform the total wobble measurement with the stirring element installed and slowly rotating through 360°. Total deflection of the probe tip must be less than 1.0 mm.
6. **Paddle Wobble** – Measure the wobble for each paddle stirring element. Use a dial test indicator to measure the wobble for the paddle shaft at a point on the shaft about 1 cm above the paddle blade with the stirring element installed and slowly rotating through 360° (see Figure 4). Total deflection of the probe tip must be less than 1.0 mm.

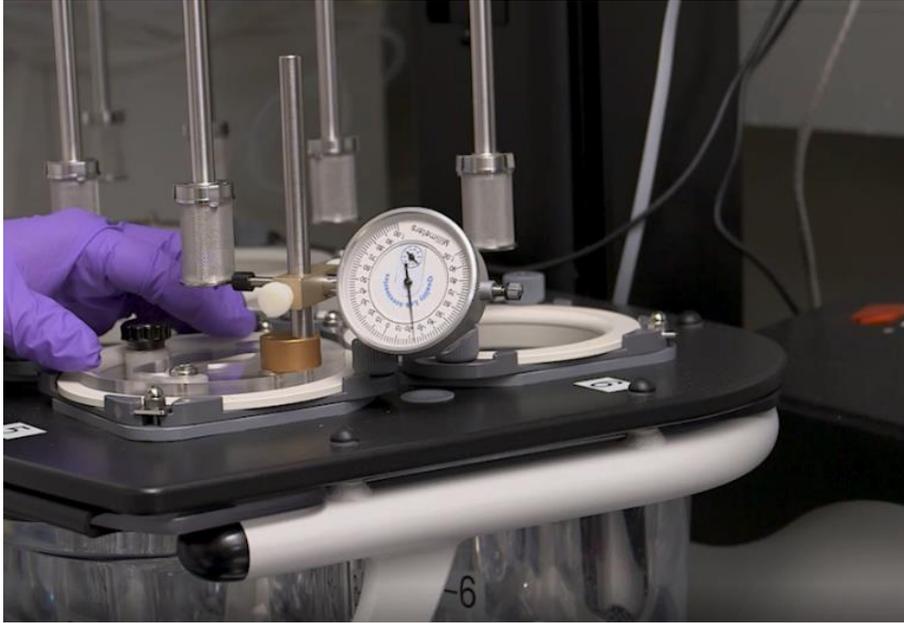


Figure 6. Dial test indicator (runout gauge) showing probe tip in contact with the bottom rim of the installed basket. (Note: the measurement of the paddle wobble is similar with the probe tip in contact with the paddle shaft within 1 cm of the top of the paddle blade).

F. *Rotation speed* – Using a digital tachometer, measure the rotation speed of all stirring element shafts. The rotation speed should be evaluated at both 50 rpm and 100 rpm. All measured speeds should be within  $\pm 1$  rpm of the set value. If during an experiment a lower or higher rotation speed is used this speed should be evaluated in the same manner with the same tolerance applied.

G. *Temperature Control* – Place vessels containing 500 mL of room temperature water in each position of the system. With the temperature control set to achieve 37.0 °C in the vessels, measure the temperature of the water in each vessel using a calibrated thermometer. After equilibration, the medium temperature measured in all vessels should agree within a range of 0.4°C (e.g., 36.7° to 37.1°).

#### IV. Performance Verification Test (PVT)

Note: The evaluation should be performed for all positions/vessels in the dissolution assembly.

A. *Reference Materials* –The Reference Materials used in the PVT (USP Dissolution Performance Verification Standard – Prednisone RS and USP Prednisone RS) should be stored as described in the respective Certificate that accompanies each lot of USP reference standard. The tablets are packaged individually in blister packs and an



additional aluminum sachet to avoid exposure to the effects of humidity. Remove tablets from the blisters at the time of use by opening the aluminum sachet, removing the blister card, and pushing the tablets through the foil backing of the blister card. Use only whole tablets.

B. *Dissolution Medium* – The PVT for Apparatus 1 and 2 uses a specific medium as described in the Certificate. The medium is deaerated.

1. ***USP Deaeration Procedure*** – Heat an appropriate volume of the medium to between 41°C to 45°C. Vacuum filter through a 0.45-µm membrane filter (HVLP type, or equivalent). Continue to stir medium under reduced pressure for an additional 5 minutes. The measured vacuum should be less than 100 mbar. Deaerated media should be handled and used with care. The dissolved gas content will tend to increase and procedures that increase the mixing of the dissolution medium or increase the area of contact between the atmosphere and the medium will tend to increase the rate of re-equilibration. A minimal time should be planned for thermal equilibration of the medium and the run should be started promptly. Other deaeration procedures are permissible, but they should be demonstrated to be equivalent to the USP procedure. This can be verified using a dissolved gas meter. Nitrogen sparging or sonication alone is not a suitable deaeration procedure and therefore should not be used.

2. ***Dissolution Media Volume*** – Dissolution Medium for USP Dissolution Performance Verification Standard – Prednisone RS – 500 mL deaerated purified water. The medium volume is measured to be within  $\pm 1\%$  of the specified value. The volume of medium stated (e.g., 500 mL) is for measurement at room temperature. As the test temperature is higher than room temperature, allowance for volume expansion on heating should be made. A more accurate and temperature independent measure of the medium volume can be obtained gravimetrically (499 g of media).

3. ***Dissolution Media Equilibration*** – With the medium-filled and vessels placed in the assembly, equilibrate the temperature of the medium to 37.0°C  $\pm 0.5^\circ$ . Measure the temperature of the medium in each vessel. The medium is equilibrated when the temperature has reached the set point and does not change between two successive readings made no less than three minutes apart (not more than 0.2° change for each vessel). Dissolution medium temperature is confirmed in each vessel upon equilibration prior to the start of the dissolution test and upon the completion of the dissolution test.

C. Dissolution Procedure

1. ***Stirring Element Height*** – Set the distance between the bottom of the vessel's inner surface and the lower part of the stirring element. Use height gauges to check the distance between the bottom of the vessel and stirring element. Measure the distance for each vessel position. Some test assemblies



allow the height of the stirring element to be set before beginning the test. All values must be set to 25.0 mm  $\pm$  2.0 mm (between 23.0 mm and 27.0 mm).

2. **Baskets** – Place one tablet in each dry basket. Attach the basket to its shaft. The test is considered to start when the basket is immersed in the medium. Immediately start the stirring after the basket is secure at the prescribed height.
3. **Paddles** – Allow the tablet to fall into the vessel in a standardized manner, e.g., along the vessel wall or at the center of the vessel along the paddle shaft. The test is considered to start when the tablet comes to rest at the bottom of the vessel. The most reproducible conditions will exist with the sample settled directly under the paddle shaft (e.g., on the vessel axis). Immediately start the stirring after the tablet has come to rest beneath the paddle.
4. **Timing** – Record the start time of the dissolution test using a calibrated timing device. The type of starting procedure must allow for sample collection and filtration of all positions within the current  $\pm$  2% tolerance limit for time ( $\pm$  36 seconds for a 30-minute run). The time needed to sample each vessel may be accommodated with a staggered start allowing a minimal start-time interval between vessels and is recommended if possible.
5. **Observations** – Carefully record any visual observations of the dissolution test, such as basket wobble, air bubble formation, and the condition or motion of the disintegrating tablet particles.
6. **Sampling** – Withdrawal and filtration of the sample aliquot conclude the test interval. After 30 minutes of testing and with rotation continuing, withdraw a portion of the dissolution medium from each vessel, about 30 mL. Samples should be withdrawn from a zone midway between the surface of the dissolution medium and the top of the basket or paddle blade, not less than 1 cm from the vessel wall.
7. **Sample Filtration** – Filter each sample immediately through a syringe filter (0.45- $\mu$ m PVDF-type or equivalent), discarding the first 5 mL portion of filtrate. [Note: Equivalent filters will provide filtrate with analytical response within 1% of the unfiltered solution. The discarded volume is a function of the filter and may not be identical to that recommended in this document.] Cool the filtered dissolution samples to ambient temperature prior to UV analysis. Do not centrifuge the sample. A separate unused filter, cannula, and clean syringe should be used for each vessel.
8. **Automated Sampling** – If used, automated sampling methods and filter probes should be validated against the manual sampling method. Variables include, carry over from system surfaces exposed to test solution, dwell time for on-line spectrophotometric analysis, line purge volume, and filter interference.



[NOTE: The sample withdrawal time tolerance ( $\pm 2\%$ ) should be maintained by the automated system sampling rate and volume.]

D. Analytical Procedure

1. **Ultra-violet spectrophotometry (UV)** - UV is used to determine the concentration of prednisone dissolved from the USP Dissolution Performance Verification Standard – Prednisone RS tablet. The absorbance of the sample solution is compared to the absorbance of the appropriate reference standard material dissolved in dissolution medium. Prepare two independent standard preparations, a working standard, and a control standard. In the absence of supporting stability data, standards should be prepared within 24 hours of use.

a) An example procedure for preparation of reference standard solutions is as follows:

Prednisone standard solution: Transfer about 25 mg of USP Prednisone RS to a 25.0 mL volumetric flask. Dissolve in approximately 10 mL alcohol (reagent grade ethanol or methanol) with sonication. After cooling to ambient temperature, dilute to volume with alcohol. Dilute the stock solution 5.0 mL in 500.0 mL with purified water to obtain a final concentration of about 0.01 mg/mL.

b) Perform UV measurements at the wavelength of maximum absorption. For prednisone use 242 nm. The solution absorbance is measured in a 1.0 cm path-length quartz cell. Using Beer’s law, the calculated absorptivity (AU per mg/mL) values of the working and control standards should agree to within 1.0% of each other.

E. **PVT study design and interpretation** – The PVT is designed to offer the choice of a single-stage or two-stage procedure. The single-stage test serves as the default procedure. The optional two-stage test is composed from the analysis of two runs of data and is applied to assemblies with less than 12 positions. The number of samples collected for assemblies of varying configurations in the single-stage or two-stage procedures is given in Table 1.

Table 1. Data set size for single-stage and two-stage testing.

Number of positions in test assembly	Number of data points		
	Single-stage test	First stage of two-stage test	Second stage of two-stage test (total)
6	12	6	12
7	14	7	14
8	16	8	16
12	12	—	—



[Note: For a twelve-position test assembly only the single-stage test is performed.]

1. **Test Results** – Calculate the percent dissolved in each vessel of the assembly. Determine the geometric mean and the % coefficient of variation (%CV). The process is as follows:

a) Single-Stage Test

1. For each position in the assembly, determine the percent dissolved at the sampling time point specified. Transform the percent dissolved results to the natural log scale and determine the mean and variance. For assemblies with 12 positions (12 dissolution vessels), no further testing is required.
2. For assemblies with fewer than 12 positions, repeat Step 1 testing with an additional set of tablets. Again, after transforming the percent dissolved results to the natural log scale, determine the mean and variance.
3. Calculate the average of the two means and of the two variances obtained in Steps 1 and 2. (Use the results from Step 1 alone for assemblies that have 12 positions.)
4. Convert the results of Step 3 to a geometric mean (GM) and percent coefficient of variation (%CV). See calculation example below for more detail.
5. Compare the results of Step 4 to the **Single-Stage** acceptance criteria in the Certificate provided with the lot of USP Dissolution Performance Verification Standard - Prednisone RS used in the test. The GM must not fall outside the ranges shown on the lot certificate and the %CV must not be greater than the limit. If both meet the criteria, the assembly has passed the PVT.

b) Optional Two-Stage Test – A laboratory may choose to implement the PVT as a Two-Stage test. The Two-Stage test is a statistically valid means of allowing the possibility of stopping the test at the first stage with a tighter GM range and lower %CV limit. The following are step-by-step instructions for the two-stage test.

1. For each position in the assembly, determine the percent dissolved at the sampling time point specified. After transforming the percent dissolved results to the natural log scale, determine the mean and variance.



2. Convert the results of Step 1 to a GM and %CV and compare to the **1<sup>st</sup> Stage of Two-Stage** acceptance criteria. The GM must not fall outside the ranges shown on the lot certificate and the %CV must not be greater than the limit. For calculation of the GM and %CV, see the calculation example below for more detail.
3. If the results of Step 2 satisfy both acceptance criteria, stop; the assembly has passed the PVT. Otherwise continue to Step 4.
4. Repeat Step 1 with an additional set of tablets and after transforming the percent dissolved results to the natural log scale determine the mean and variance for the data obtained at this step.
5. Average the two means and two variances obtained in Steps 1 and 4.
6. Convert the results of Step 5 to a geometric mean (GM) and percent coefficient of variation (%CV). For calculation of the GM and %CV, see the calculation example below for more detail.
7. Compare the results of Step 6 to the **2<sup>nd</sup> Stage of Two-Stage** acceptance criteria. The GM must not fall outside the ranges shown on the lot certificate, and the %CV must not be greater than the limit. If both meet the acceptance criteria, the assembly has passed the PVT.

c) Calculation example (expressed as Microsoft Excel<sup>®</sup> worksheet functions):

Run 1:  $x_1, x_2, \dots, x_n$  in natural log scale:  $\text{Ln } x_1, \text{Ln } x_2, \dots, \text{Ln } x_n$

Run 2:  $x_{n+1}, x_{n+2}, \dots, x_{2n}$  in natural log scale:  $\text{Ln } x_{n+1}, \text{Ln } x_{n+2}, \dots, \text{Ln } x_{2n}$

1<sup>st</sup> Stage of Two-Stage test for n = 6, 7, or 8 and Single-Stage for n = 12:

$\text{GM1} = \exp(\text{average}(\text{Ln } x_1: \text{Ln } x_n))$

$\%CV = 100 * \text{sqrt}(\exp(\text{var}(\text{Ln } x_1: \text{Ln } x_n)) - 1)$

Single-Stage or 2<sup>nd</sup> Stage of Two-Stage for n = 6, 7, or 8:

$\text{GM} = \exp(\text{average}(\text{average}(\text{Ln } x_1: \text{Ln } x_n), \text{average}(\text{Ln } x_{n+1}: \text{Ln } x_{2n}))) = \exp(\text{average}(\text{Ln } x_1: \text{Ln } x_{2n}))$

$\%CV = 100 * \text{sqrt}(\exp(\text{average}(\text{var}(\text{Ln } x_1: \text{Ln } x_n), \text{var}(\text{Ln } x_{n+1}: \text{Ln } x_{2n}))) - 1)$

d) Criteria – The geometric mean and %CV for the data from the dissolution procedure are compared with the appropriate acceptance criteria. The acceptance criteria are given on the Certificate for the lot of USP Dissolution Performance Verification Standard – Prednisone RS used. [Note: All values should be calculated based on the label claim for each of the USP Dissolution Performance Verification Standard – Prednisone RS tablets used (i.e., 10 mg for USP Dissolution Performance



Verification Standard – Prednisone RS). The actual tablet weight is not relevant for the calculations.]

e) A web tool that can be used to perform the calculation is available at the USP Website (<https://apps.usp.org/app/USPNF/pvtCalculationTool/>)

2. **Periodicity/Frequency** – USP recommends the following periodicity associated with mechanical calibration and Performance Verification Testing procedures.

- a) Mechanical calibration: Performed at six-month intervals
- b) Performance Verification Test: Performed at six-month intervals. The PVT for a specific apparatus is required if that apparatus is used in the test assembly. Both Apparatus 1 and 2 need only be evaluated if both Apparatus are used in the test assembly.
- c) Mechanical calibration and PVT should also be performed upon installation, relocation, replacement of individual elements (e.g., vessels, baskets and or paddles) or repair of assembly.