# Dissolution Toolkit
# Procedures for
# Mechanical Calibration and Performance Verification Test
# Apparatus 1 and Apparatus 2
# Version 2.0
# March 22, 2010

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Scope:
The dissolution toolkit provides a description of best practices associated with the mechanical calibration and performance verification test for the USP basket and paddle dissolution apparatuses and test assemblies. The best practices have been developed based on experience gained by the USP laboratory (9, 13, 14, 15) and with suggestions from the USP Expert Committee on Biopharmaceutics. While not a standard requiring rigid compliance, the dissolution toolkit is intended to provide information aiding the dissolution laboratory in the effort to obtain valid dissolution testing results.

Audience:
Scientists, chemists, and technicians, lab managers with practical experience of dissolution testing who perform and evaluate the performance verification test.

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

Analytical instrumental qualification (AIQ), which includes installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ), is widely accepted. 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 Prednisone Reference Standard Tablets.

CONTENTS

# MECHANICAL CALIBRATION

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.

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 not more than 1°. The influence of bench top surface inclination on the dissolution assembly is compensated by leveling devices (see Component Conformance, Vessel Support Base below).

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 in the same test assembly for all dissolution runs. For ease of identification and record keeping, apparatus positions on the vessel support plate of the dissolution test assembly should be identified systematically.

Component Conformance

*Basket (Apparatus 1*)—Basket dimensions must conform to <711> Dissolution, Figure 1. 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 (0.5 mm deviation over 37 mm height is about 1 degree). The mesh has no gross defects.

*Paddle (Apparatus 2)*—Paddle dimensions must conform to Figure 2 in <711>. 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 and otherwise intact.

*Vessel* —Vessels conform to dimensional requirements of <711> Dissolution. Use a vernier caliper or depth gauge. The vessel inner surfaces are clean, without gross etching or scratches.

*Vessel Support Plate (Base plate)*—A spirit level may be used. Base plate inclination is not more than 0.5° in each of two orthogonal directions.
Figure 1 shows that a reading closer to 0.0° can be achieved. 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 be considered. Thus the levelness of the vessel support base should be confirmed 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 1. Electronic level giving 0.0˚ reading on the base plate of a test assembly.

## Alignments

*Shaft verticality*—Use a digital protractor to check the verticality of the stirring elements. Measure the verticality for each stirring element in two orthogonal positions (see Figure 2). 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.

*Vessel verticality*—Use a digital protractor to check the verticality of the vessels in the dissolution assembly. Measure 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.

*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 not more than 2 cm below the vessel flange. 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.

Alternatively, the centering can be measured using an inside divider to obtain a distance and measuring the distance with a vernier caliper or a micrometer (see Figure 3). Where this alternative method is used, measure the distances from the shaft to the inner vessel wall at four locations equally spaced around the vessel and no more than 2 cm below the vessel flange (see Figure 3). The difference between the largest and smallest readings is not greater than 2.0 mm.

*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. 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.

*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 2. Measurement of the verticality of the stirring element using digital protractor.

## Motor and Transmission

*Rotation speed*—Measure the rotation speed of all stirring element shafts using a tachometer. The rotation speed should be evaluated at both 50 rpm and 100 rpm. All measured speeds should be within ± 1 rpm of the set value.

## 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°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°).

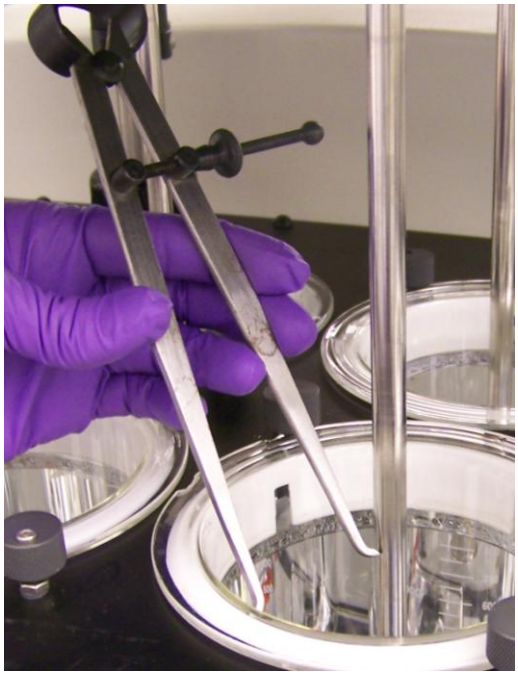

Figure 3. Used in alternative centering determination, here an inside divider is used to acquire distance from inside vessel to shaft. The distance between the divider contact points is measured by means of a vernier caliper or micrometer.


Figure 4. Dial test indicator (runout gauge) showing probe in contact with installed paddle shaft (Note that the measurement of basket wobble is similar with the probe tip in contact with the bottom basket rim). A different probe tip design may be used such as a large flat tip.

## PERFORMANCE VERIFICATION TEST

The evaluation should be performed for all positions/vessels in assembly.

Reference Materials—
USP Prednisone Tablets RS
USP Prednisone RS

The Reference Materials used in the PVT should be stored as described in the respective Certificate.

Dissolution Medium—

The PVT for Apparatuses 1 and 2 uses a specific medium as described in the Certificate. The medium is deaerated.

> *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. For testing with USP Prednisone Tablets RS, a dissolved oxygen level of not more than about 6 ppm has been shown to be acceptable.

Volume is measured to be within ± 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 expansion on heating should be made. A more accurate and temperature independent measure of the medium volume is through weight.

With the medium-filled vessels placed in the assembly, equilibrate the temperature of the medium to 37°C ±0.5°. Measure the temperature of the medium in each vessel. The medium is equilibrated when the temperature has reached the setpoint 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 and upon the completion of the dissolution test.

Dissolution Medium for *Prednisone Tablets RS* —500 mL deaerated purified water. (See section on deaeration above.)

Nitrogen sparging is not a suitable deaeration procedure and therefore should not be used.

Dissolution Procedure—

*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 within 23.0 and 27.0 mm.

*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 at the prescribed height. Immediately start the stirring.

*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.

*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 ± 2% tolerance limit for time (± 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.

*Observations*—Carefully record any visual observations of the dissolution test, such as basket wobble, air bubble formation, or the condition or motion of the disintegrating tablet particles.

*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. Sample from a zone midway between the surface of the dissolution medium and the top of the basket or top of the paddle blade, not less than 1 cm from the vessel wall.
Filter each sample immediately through a syringe filter (0.45-µm 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. Discard 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 (sample and standard solutions are at the same temperature). Do not centrifuge the sample. A separate unused filter, cannula, and clean syringe should be used for each vessel.

> *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, and filter interference.

Analytical Procedure—

Ultra-violet spectrophotometry (UV) is used to determine the concentration of prednisone dissolved from the Reference Standard 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. Prepare the standards within 24 hours of use. 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 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.

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 be in agreement with historic values and within 1% of each other. Additional information on spectrophotometric analysis can be found in <851> Spectrophotometry and Light Scattering.

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 configuration in the single stage or two stage procedures is given in the following table.

Data set size for single and two stage testing

| | Number of data points | | |
|---|---|---|---|
| Number of positions in test assembly | 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 that for twelve position test assembly only the single stage test is performed.]

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.

## 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 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. The GM must not fall outside the limits, and the %CV must not be greater than the limit. If both meet the criteria, the assembly has passed the PVT.

## 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 %CV requirement. 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 **1st Stage of Two-Stage** acceptance ranges. The GM must not fall outside the limits, and the %CV must not be greater than the limit. For calculation of the GM and %CV, see calculation example for more detail.
3. If 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 calculation example for more detail.
7. Compare the results of Step 6 to the **2nd Stage of Two-Stage** acceptance ranges. The GM must not fall outside the limits, and the %CV must not be greater than the limit. If both meet the acceptance criteria, the assembly has passed the PVT.

**Calculation example** (expressed as Microsoft Excel® worksheet functions)**:**

Run 1: $x_1, x_2, ..., x_n$ in natural log scale: Ln $x_1$, Ln $x_2$, ..., Ln $x_n$

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

1st Stage of Two-Stage for n=6, 7, 8 and Single-Stage for n=12:

GM1 = exp(average (Ln $x_1$:Ln $x_n$))

%CV1 = 100*sqrt(exp(var(Ln $x_1$:Ln $x_n$)) -1)

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

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

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

exp: exponential ($e^x$) var: variance sqrt: square root *: multiply

100: conversion factor to percentage

## Criteria

The geometric mean and %CV for the data from the dissolution procedure are compared with the appropriate acceptance limits. The acceptance limits are given on the Certificate for the RS Tablet used.

[All values should be calculated based on the label claim for each of the Reference Standard Tablet (10 mg for Prednisone Tablets RS). The actual tablet weight is not relevant for the calculations.]

A webtool that can be used to perform the calculation is available on USP's Website (www.USP.org)

## PERIODICITY/FREQUENCY

USP recommends the following periodicity associated with mechanical calibration and Performance Verification Testing procedures.

- Mechanical calibration: six month intervals
- Performance Verification Test: six month intervals. PVT for a specific apparatus is required if that apparatus is used in the test assembly. Both Apparatuses 1 and 2 need be

evaluated only if both Apparatuses are used in the test assembly.

- Mechanical calibration and PVT should be performed upon installation, translocation, or repair of assembly.

## NOMENCLATURE

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 motion 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 apparatuses are grouped in a dissolution test assembly.

Stirring Element: A paddle, rotating basket and shaft, or other device for promoting the movement of 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 apparatuses providing temperature control, controlled unified motion of stirring elements, and providing the opportunity for simultaneous or individual start of the apparatuses.

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.

Drive Unit Plate: Support structure for the drive mechanism 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. The removable drive unit cover will not be typically considered to represent a suitable surface on which the level of the drive unit plate can be determined.

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 the dissolution sample aliquot preparation procedure. 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.

# REFERENCES


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# APPENDIX

## Equipment Used in Mechanical Calibration and PVT

Spirit level—is used to measure the inclination of an object and to level machines. A true spirit level uses the observed position of a bubble with respect to fiducial lines in a fluid-filled tube to indicate level or plumb. A digital protractor indicates degrees of inclination measured by electronic means.

Tachometer—measures rotation rate in revolutions per minute. Tachometers may be mechanical (rotation transferred and measured directly by device) or electronic (frequency of light reflections or induced electromagnetic frequency measured by device). Tachometers can capture average rotational speed over desired intervals.

Caliper—measures distance between two opposing points or surfaces. The trueness and precision of measurement by a caliper can be checked using gauge blocks. Gauge blocks are standardized materials that represent a range of distances and are used as reference distances for calibration of measuring tools.

Compass (Inside divider as in Figure 4)—transfers a distance from an otherwise inaccessible position to a location where the distance can be determined using a caliper. Compasses can have inward or outward-facing points to allow the transfer of inner or outer distances. The tips of the compass are adjusted to fit across the points to be measured and fixed, the compass is then removed, and the distance between the tips measured.

Centering gauge—determines the orientation within the vessel of the stirring shaft with respect to the centerline. Centering of shaft in the vessel can be estimated by attaching a specially designed dial test indicator to the stirring element shaft that then allows the measurement of the distance from the shaft to the vessel. Accuracy of distances given by this gauge may be checked with a caliper. Alternatively a compass and caliper can be used. The compass is used to transfer the distance so that it can be measured by the caliper. Specially designed calipers are also available that can measure the distance between inaccessible points such as between the inner walls of a dissolution vessel.

Dial test indicator (Runout gauge)—used to measure the eccentricity of a rotating surface. Trueness and precision of the indicator reading can be checked with a caliper, feeler gauge or gauge block.

Height gauges—allow the distance between the bottom of the stirring element and the inside bottom of the vessel to be set. Stirring element height gauges can be either designed to act as gauge blocks or calipers. The gauge-block designs, having a fixed 25-mm distance between opposing surfaces, are inserted in the space of interest with the distance verified by touch (go/no-go). The caliper-style height gauge is similarly placed but acting as a caliper the actual distance can be measured.

Thermometer—measures the temperature of the water bath and dissolution medium in the vessels for PVT (see <21> Thermometers)

Feeler Gauge—these are small lengths of metal, typically of steel, of different thicknesses with measurements marked on each piece used to provide a standard thickness. Feeler gauges can be used as standard thicknesses to verify the reproducibility and repeatability of measurements by calipers and dial test indicators.

Gauge blocks—typically represent larger thicknesses than provided by feeler gauges and are used where a greater standard thickness is appropriate.