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STIMULI TO THE REVISION PROCESS

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USP Guideline on Procedures for Mechanical Performance Qualification for USP Apparatus 3 – Reciprocating Cylinder

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ABSTRACT

This USP guideline represents the current best practices for determining mechanical qualification performance for USP apparatus 3, described in Dissolution <711>. The guideline covers the performance qualification topics of environment, benchtop levelness, assembly, apparatus conformance, alignments, drive system and transmission, temperature control, component certification, periodic preventative maintenance, physical parameter measurement, and operational checks. This guideline is intended to provide information that aids the dissolution laboratory in establishing appropriate standard operating procedures to verify compliance with compendial requirements and ensure valid dissolution and drug release testing results.

USP welcomes proposals for a drug product that could be used as a final performance qualification to assess the overall suitability of the equipment.

INTRODUCTION

This guideline outlines best practices for the mechanical performance qualification of the USP apparatus 3 - reciprocating cylinder. The best practices have been developed on the basis of experience gained by the USP laboratory and with suggestions from the Performance Verification Testing Standard Expert Panel under the guidance of the USP General Chapters—Dosage Forms Expert Committee. While not a standard requiring rigid compliance, this guideline is intended to provide information that aids the dissolution laboratory in establishing appropriate standard operating procedures to verify compliance with compendial requirements and ensure valid dissolution and drug release testing results.

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 by the USP.

Analytical instrumental qualification (AIQ), which includes installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ), is widely accepted. For dissolution assemblies, the mechanical qualification steps outlined in this guide should satisfy the OQ and parts of Analytical Instrument Qualification <1058>.

The USP Chlorpheniramine Maleate Extended Release Tablets RS used in the performance verification tests (PVTs) for USP Apparatus 3 was discontinued effective February 2012. Because there is no replacement USP PVT for the reciprocating cylinder apparatus at this time, a mechanical means of apparatus qualification may be used to demonstrate that the apparatus is suitable for its intended use.

USP is seeking proposals for drug products that could be used in the PVT of USP Apparatus 3. These drug products should have a modified-release mechanism compatible with the functioning of USP Apparatus 3—for example, not disintegrating completely in the first row of the apparatus and exhibiting a release rate that allows for two or more sampling time points over a reasonable test length. Please address any suggestions to Margareth R. C. Marques at mrm@usp.org.

DEFINITIONS

Agitation Element

An *agitation element* is the shaft for attaching the reciprocating cylinder containing the dosage form. The up-and-down motion provides agitation to promote the movement of the dissolution medium through the reciprocating cylinder relative to the dosage unit under test.

Apparatus

An *apparatus* is the basic unit for the in vitro performance testing of dosage units. The apparatus consists of a container (vessel) for the dosage unit and the dissolution medium, a device for promoting motion of the dissolution medium (agitation element), temperature control, and a support to hold the vessel and reciprocating element in a fixed orientation. Typically, 6–8 apparatuses are grouped in a dissolution test assembly.

Assembly

An *assembly* is a combination of multiple positions within the apparatus that provide temperature control; controlled sinusoidal motion of the reciprocating shafts; and the capability for simultaneous starting, stopping, and movement of the reciprocating cylinders from row to row. The time required for the reciprocating shafts for the upward stroke is equal to the time required for the downward stroke, and the change in stroke direction is a smooth transition, rather than an abrupt reversal of motion.

Base Plate

The *base plate* is the structural element or frame of the test assembly that fixes and provides support for the removable vessel plates during testing. Vessel support plates may be permanently incorporated into the base or removable from the base.

Calibration

Calibration is a process, performed under a set of specified and controlled measurement conditions, that establishes a relationship between the indication or output of the measurement device (with measurement uncertainties) and accepted measurement standards (with their corresponding indications and associated measurement uncertainties; see Dissolution <711>).

Dissolution System

The *dissolution system* includes USP Apparatus 3, which may be connected to a sampling and filter unit and may include on-line instrumentation such as a UV–Vis spectrophotometer or an HPLC system.

Drive Unit Plate

The *drive unit plate* is a support structure that holds the drive mechanism for the reciprocating elements. The moving parts of the drive unit are protected from contamination by a cover that also shields against operator injury. The removable drive unit cover is not typically considered a suitable surface to determine the levelness of the drive unit plate.

Position

The *position* is the location within the USP Apparatus 3 test assembly where a particular vessel and reciprocating cylinder are situated (e.g., row 1, vessel 1).

Run

A *run* is common terminology for the dissolution sample aliquot preparation procedure. As stated in <711>, Interpretation, the smallest sample set tested comprises 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.

Vessel Support Plates

Vessel support plates should hold vessels in place during the test. Vessel plates may be removable but should be returned to their original location if removed and replaced.

PERFORMANCE QUALIFICATION

Environment

Benchtops are used to support dissolution equipment. A suitable benchtop must be level and sturdy and provide a high inertial mass to limit vibration. Disturbances, such

as the placement of containers holding large volumes of solution, may produce transient vibrations but should not affect the levelness of the surface.

Benchtop Levelness

A digital or spirit level should be used to measure the inclination of the benchtop in two orthogonal directions. Benchtop surface inclination should be no more than 1°. The influence of benchtop surface inclination on the dissolution assembly can be compensated for by leveling devices (see Apparatus Conformance and Vessel Plates sections below).

Assembly

All vessels and reciprocating cylinder components should meet USP specifications and be dedicated to each test assembly for all dissolution runs. For ease of identification and recordkeeping, apparatus positions on the vessel support plate of the dissolution test assembly should be identified systematically.

Apparatus Conformance

Vessel and Reciprocating Cylinder Components

Vessels and reciprocating cylinder components conform to the dimensional requirements of <711>, as shown in Figure 1. Use a Vernier caliper, depth gauge, or other suitable measurement devices to confirm that the measurements meet the specifications. The vessels' inner surfaces must be clean, without significant etching or scratches.

Vessel Plates

A spirit level may be used on the frame supporting the removable vessel plates. The inclination is not more than 0.5° in each of two orthogonal directions. Figure 2 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. If the apparatus is not level after maximum adjustment, it should be moved to a more level area. The strain on the test assembly structure due to the mass of the filled water bath and vessels should be taken into account. Thus, the levelness of the vessel support frame should be confirmed with the water bath filled. The condition of the removable vessel support plate(s) should be visually evaluated and confirmed to be uniform, even, and free of distortion or deformation. The removable vessel support plate(s) should resist deformation when under load by filled vessels and should remain level. The vessel support plate(s) should not be corroded to a point where vessel perpendicularity may be jeopardized.

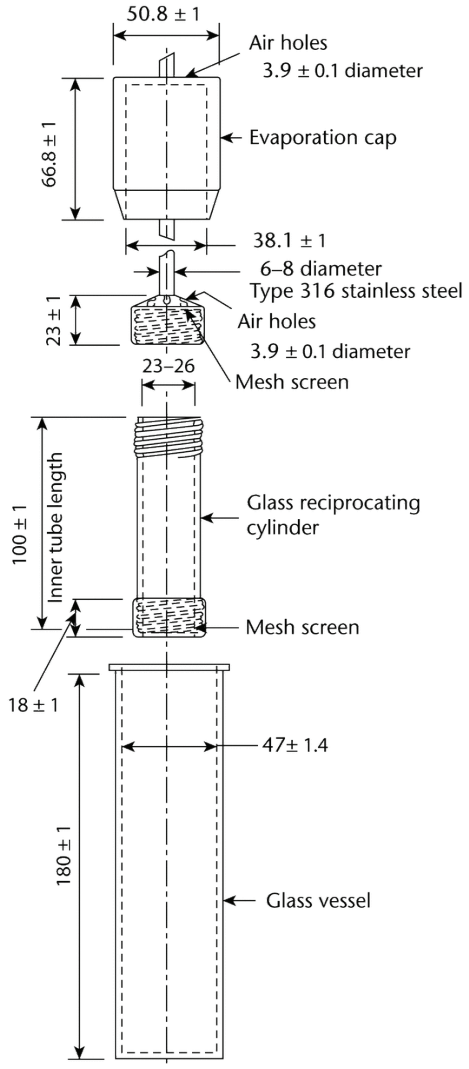

Figure 1. Apparatus 3 - reciprocating cylinder. All measurements are expressed in millimeters unless otherwise noted.

Alignments

Shaft Verticality

Use a digital protractor (level) to check the verticality of the reciprocating shafts. Measure the verticality for each shaft in two vertical planes at 90.0° angles to each other (see Fig. 3). The deviation should be no more than 0.5° from 90.0° for these measurements.

Vessel Verticality

With the vessels in their run position, place a machinist square into the vessel, taking care not to scratch the surface, and place a digital level or spirit level on the perpendicular surface to determine vessel verticality (Fig. 4). Note that excess pressure on the wall of the vessel may misalign the vessel, causing inaccurate

Figure 2. Electronic level on the USP apparatus 3 vessel plate.

measurement. Measure the verticality for each vessel in two positions oriented at 90.0° around the vessel axis. The ideal reading obtained on a horizontal surface of the machinist square is 0.0°. The deviation should be no more than 0.5° from 0.0° for this measurement. No part of the assembly, including its surrounding environment, should contribute motion, agitation, or vibration other than that caused by the smooth, vertically reciprocating shaft.

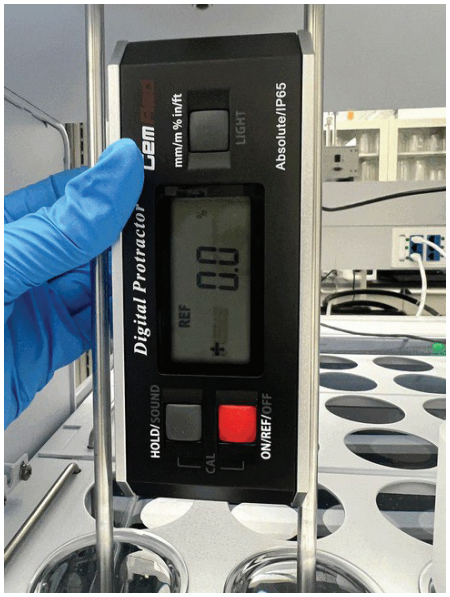

Figure 3. Electronic level to determine shaft verticality of apparatus 3.

Drive System and Transmission

Reciprocation Rate

Measure the reciprocation rate of all shafts using a calibrated timer or digital tachometer (see Fig. 5). The reciprocation rate should be evaluated at both 10 and 50 dips per minute (dpm) or in a range to cover the methods used on the instrument. The calibration range should be stated on the calibration label affixed to the instrument. All measured speeds should be within ± 5% of the set rate.

Temperature Control

Place vessels containing 250 mL of water in each position of the system. With the temperature control set to achieve 37.0° in the vessels and the shafts and evaporation caps lowered into position, measure and document the temperature of the water in each vessel using a calibrated thermometer once they have had time to equilibrate. After equilibration, the medium temperature measured in all vessels should agree within a range of 0.5° and within ± 0.5° of the set temperature.

QUALIFICATION PROCEDURES

Relying on an enhanced mechanical qualification approach, in the absence of a PVT for the USP apparatus 3 - reciprocating cylinder, these mechanical steps should be performed periodically at a frequency determined by an internal risk assessment to maintain the apparatus in a qualified state.

The following steps should be implemented to ensure a current state of qualification of the reciprocating cylinder apparatus: certification of components, documentation of scheduled preventative maintenance, mechanical qualification parameter measurement, and operational checks to be performed at the time of testing.

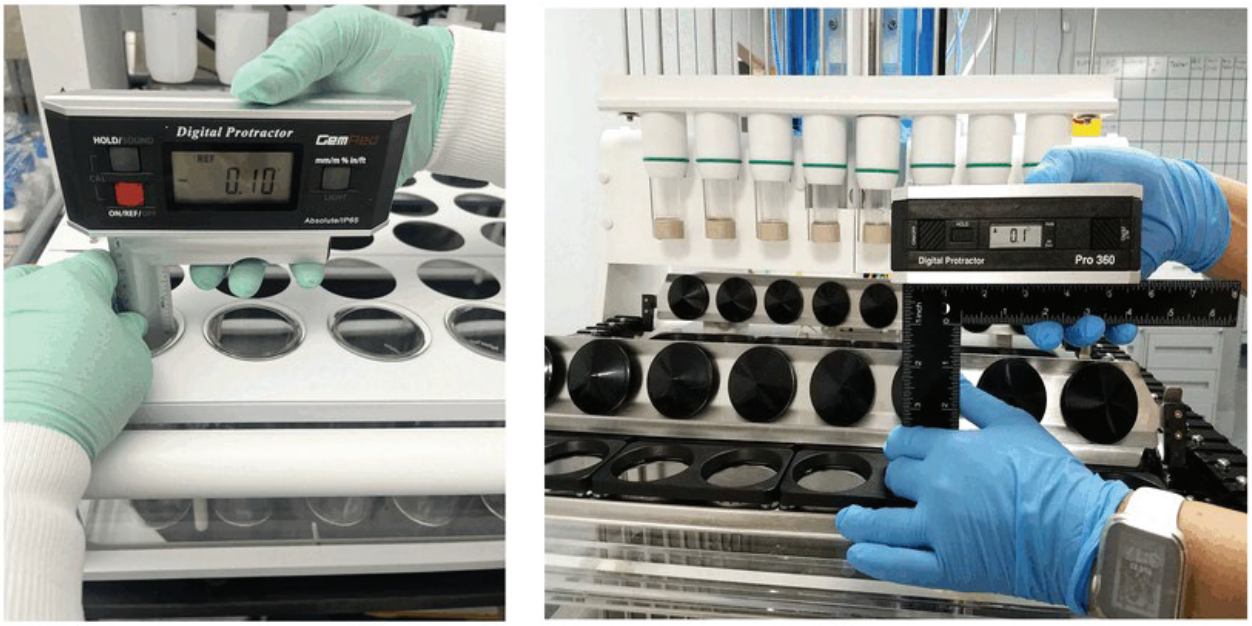

Figure 4. Measurement of apparatus 3 vessel verticality.

Figure 5. Digital measurement of the reciprocation rate. (Printed with permission of Logan Instruments).

Component Certification

Documentation should be established for each reciprocating cylinder apparatus component to demonstrate that it meets the specifications and tolerances according to <711> (see Fig. 1 and Table 1). Certificates of conformance (CoCs) with actual measurements and acceptance criteria may be obtainable from dissolution apparatus manufacturers. If certificates are unavailable, conformance measurements may be conducted by the end user and documented. Regarding screens used for analysis, screen sizes are described in standards such as ASTM E11-09 and ISO 3310-1:2016 (*1*, *2*).

(NOTE—Specialized tools may be required to measure screen size and the internal diameter of the reciprocating cylinder.)

Table 1. Specifications and Tolerances for Reciprocating Cylinder Apparatus Component

Component	Specification and Tolerance		Material of Construction
Shaft	Diameter: 7 ± 1 mm	—	Inert (e.g., SS316[a])
Vessels	Height: 180 ± 1 mm	Inner diameter: 47 ± 1.4 mm	Inert (e.g., glass)
Reciprocating cylinders	Height: 100 ± 1 mm	Inner diameter: 25 ± 2.0 mm	Inert (e.g., glass)
Upper cap	Height: 23 ± 1 mm	Air hole diameter: 3.9 ± 0.1 mm	Inert (e.g., polypropylene)
Lower cap	Height: 18 ± 1 mm	—	Inert (e.g., polypropylene)
Evaporation cap	Height: 66.8 ± 1 mm Outer diameter: 50.8 ± 1 mm	Inner diameter: 38.1 ± 1 mm Air hole diameter: 3.9 ± 0.1 mm	Inert
Screens	As defined in the specific method or monograph	If not specified, use dimensions from ASTM or ISO standards	Inert (e.g., SS316 or polypropylene)

[a]*SS316 = Stainless steel grade 316.*

Preventive Maintenance

The apparatus must undergo periodic maintenance (PM) to ensure it is in proper condition. The PM intervals are to be determined by the quality system and usually coincide with the periodic qualification of the apparatus. Manufacturer recommendations for PM—including cleaning, lubrication, and replacement of parts—should be followed. (NOTE—The apparatus should be disconnected from the power source before doing any maintenance, and these steps should only be performed by qualified or trained maintenance personnel.)

- Inspect the condition of vessels, cylinders, caps, and agitator shaft O-rings.
- Ensure that vessel evaporation covers do not disrupt the centering of the glass vessels.
- Clean and lubricate the horizontal guides and agitator shafts with the recommended lubricant, as directed by the manufacturer. Evaluate internal components by unplugging and removing the outer cover to examine:
  - Belt for damage or wear
  - Belt tension specific to the manufacturer's recommended specification
  - Lubricate arms and mechanical linkages with the recommended lubricant as directed by the manufacturer
- Check communication and control cables, as well as power cords, which should not show signs of wear, damage, or corrosion.
- Check the bath heater, circulator, and tubing for blockage, damage, or algae growth; replace as needed.

Physical Parameter Measurement

The following operating parameters must be periodically measured to ensure the apparatus is operating in a qualified state:

- Vessel temperature: 37.0 ± 0.5 °C
- Dip rate: ± 5% of set speed
- Stroke distance: 10.0 ± 0.1 cm
- Bottom screen: Per method, dimensions subject to ASTM 3 or ISO 4
- Top screen: Per method (optional), dimensions subject to ASTM 3 or ISO 4
- Time points: ± 2% of the specified time to start sampling

Stroke Distance

Depending on the apparatus design, the assembly manufacturer may provide a calibrated caliper to be mounted onto the dipping manifold or shaft to measure the stroke distance of the reciprocating apparatus, as shown in Figure 6. For instruments without a measurement tool, apply tape to the vertical shaft assembly and place a mark on the tape as it reciprocates using a fine-tip marker. The tape may be temporarily left in place and measured or removed and recorded in a logbook. After placing the mark on the tape, measure the length of the mark with a calibrated caliper, as shown in Figures 7 and 8. Alternatively, other appropriate digital tools may be used.

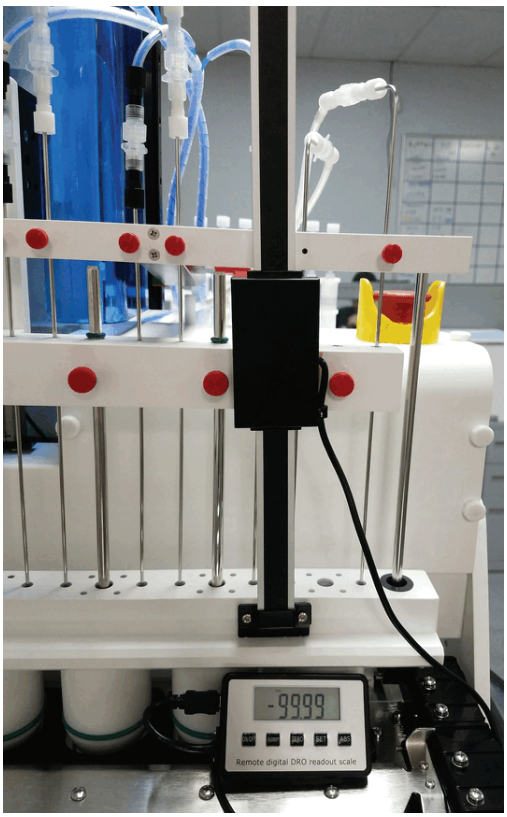

Figure 6. Digital caliper for measuring stroke distance. (Printed with permission of Logan Instruments).

Operational Checks

Before each run with USP apparatus 3, the analyst should perform and document the following checks on the apparatus to ensure that it is suitable for its intended purpose:

1. Reciprocating cylinders' glass surfaces are free from residue, scratches, and cracks.
2. Screens are the appropriate dimension required by the method and are not damaged, frayed, misshapen, or corroded.

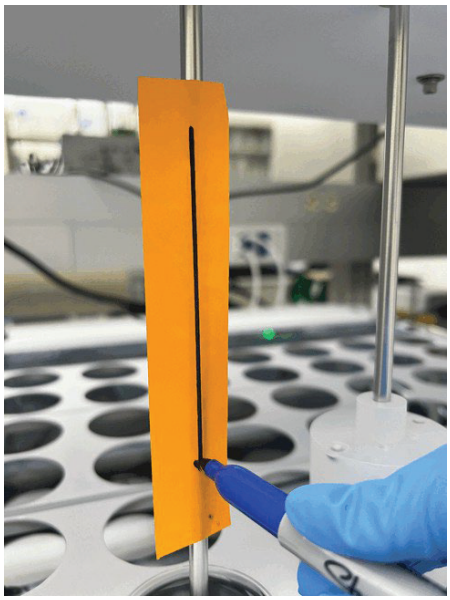

Figure 7. Recording stroke distance with fine-tip marker.

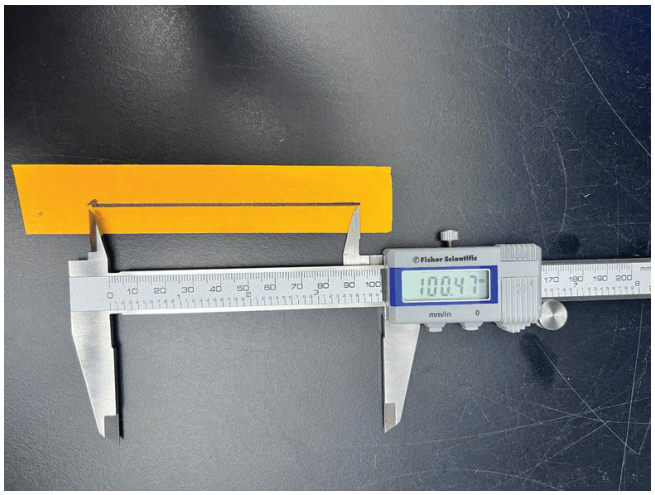

Figure 8. Measuring stroke distance with a calibrated caliper.

3. Vessels are clean and free from residue, scratches, and cracks.
4. Vessels remain stationary during the test.
5. Upper and lower caps are clean and free from residue.
6. Vessel temperature is maintained at 37.0 ± 0.5 °C (beginning and end of run).
7. Evaporation covers are properly fitted to allow shafts to reciprocate freely without moving the evaporation cover or pushing the vessel off center while the cylinder is reciprocating. Proper evaporation control should be maintained for all vessels and positions.

Periodicity and Frequency

USP recommends the following periodicity associated with mechanical calibration:

1. Scheduled mechanical qualification of the apparatus should be performed at a frequency determined by the quality system or after repair, movement, or relocation of the apparatus.
2. Once the apparatus meets the acceptance criteria included in <711>, the instrument is considered qualified. (NOTE—There is no current USP PVT for apparatus 3.) Prior to each test, the analyst should perform and document the operational checks outlined above.

APPENDIX

Equipment Used in Mechanical Calibration

Caliper

A *caliper* measures the distance between two opposing points or surfaces. The trueness and precision of caliper measurements can be checked using gauge blocks. Gauge blocks are standardized materials that represent specific distances and are used as reference standards for calibrating measuring tools.

Digital Protractor or Digital Level

A *digital protractor or digital level* is used to measure the inclination of an object. A digital protractor indicates degrees of inclination by electronic means and provides a more precise measurement compared with spirit or bubble levels.

Stopwatch

A *stopwatch* is a calibrated, traceable timing device used to measure reciprocation rate or dips per minute (dpm).

Thermometer

A *thermometer* is a calibrated device used to measure the temperature of the water bath and dissolution medium in the vessels.

DISCLAIMER

Certain commercial equipment, instruments, vendors, or materials may be identified in this article to specify adequately the experimental procedure. Such

identification does not imply approval, endorsement, or certification by USP of a particular brand or product, 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.

REFERENCES

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2. ISO 3310-1:2016: Test Sieves—Technical Requirements and Testing—Part 1: Test Sieves of Metal Wire Cloth. The International Organization for Standardization; 2016.