
Guidance for Industry

The Use of Mechanical Calibration of Dissolution Apparatus 1 and 2 – Current Good Manufacturing Practice (CGMP)

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

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Current Good Manufacturing Practices (CGMP)**

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I. INTRODUCTION

This guidance is intended to aid drug manufacturers (including ancillary testing laboratories) in calibrating U. S. Pharmacopeia (USP) Dissolution Apparatus 1 and 2 to help assure that critical parameters associated with the dissolution apparatus meet certain *mechanical calibration* (MC) tolerances. This guidance recommends that an *enhanced* MC procedure (such as the one recommended in this guidance) can be used as an alternative to the current *Apparatus Suitability* procedure for Dissolution Apparatus 1 and 2 described in USP General Chapter <711> *Dissolution*. Regardless of whether the enhanced MC procedure or *Apparatus Suitability* procedure is used, the guidance also recommends that appropriate measures be taken to control the following sources of significant variability in dissolution testing: dissolved gases, vibration, and vessel dimensions.

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¹ This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA).

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II. BACKGROUND

FDA's current good manufacturing practice (CGMP) regulations require that laboratory apparatus be calibrated at suitable intervals in accordance with an established written program of scheduled procedures (21 CFR 211.160(b)(4) and 211.68). The enhanced MC procedure recommended in this guidance can be used as an alternative to the current *Apparatus Suitability* procedure for USP Dissolution Apparatus 1 and 2 described in USP General Chapter <711> *Dissolution*. The Chapter <711> Apparatus Suitability procedure requires that the dissolution apparatus assembly meet certain MC tolerances and that a performance verification test (PVT) be performed with specified USP Reference Standard (RS) tablets; however, the MC tolerances specified in USP <711> for the dissolution apparatus assembly are not as comprehensive or as stringent as those in the enhanced MC procedures recommended in this guidance.

Recent studies performed in FDA and USP laboratories have identified several different sources of variation within Apparatus 1 and 2 that can be minimized by employing an enhanced MC procedure. In 1996, the Pharmaceutical Research and Manufacturers of America (PhRMA) Dissolution Committee formed a Subcommittee on Dissolution Calibration. In 2000, the subcommittee published a *Stimuli* article in the *Pharmacopeial Forum* in which it recommended "enhanced mechanical calibration" as a value-added means for maintaining dissolution apparatus in a state of calibration.² The use of an enhanced mechanical calibration procedure to satisfy the CGMP calibration requirement (§ 211.160(b)(4)) was endorsed by FDA's Advisory Committee on Pharmaceutical Science (ACPS) on October 25, 2005,³ following a presentation by FDA's Center for Drug Evaluation and Research (CDER), Division of Pharmaceutical Analysis (DPA). DPA reported its findings from a gauge repeatability and reproducibility study showing that a significant amount of the observed variability in the dissolution test data was attributable to centering differences among the six dissolution vessels.⁴ In another study, DPA showed that vessel-to-vessel variability can be minimized by assuring that mechanical variables are controlled and by performing dissolved gas measurements to provide assurance of adequate deaeration of dissolution media before test samples are introduced.⁵ Subsequently, studies performed by USP using dissolution Apparatus 1 and 2 also identified several variables that contributed to the overall variation of the observed dissolution test results.^{6,7} These studies

² PhRMA Subcommittee on Dissolution Calibration: Oates M, Brune S, Gray V, Hippeli K, Kentrup A et al., July-Aug 2000, Dissolution Calibration: Recommendations for Reduced Chemical Testing and Enhanced Mechanical Calibration, *Pharmacopeial Forum*; 26(4): 1149-1151.

³ Pharmaceutical Science Advisory Committee Meeting, October 25-26, 2005, transcript available at <http://www.fda.gov/ohrms/dockets/ac/cder05.html#PharmScience>.

⁴ Gao Z, Moore TW, Smith AP, Doub W, Westenberger B and Buhse L, 2007, Gauge Repeatability and Reproducibility for Accessing Variability During Dissolution Testing: A Technical Note, *AAPS PharmSciTech*; 8(4): E1-E5.

⁵ Gao Z, Moore TW, Doub WH, Westenberger BJ, Buhse LF, 2006, Effects of Deaeration Methods on Dissolution Testing in Aqueous Media: A Study Using a Total Dissolved Gas Pressure Meter, *Journal of Pharmaceutical Science*; 95(7): 1606-1613.

⁶ Eaton J, Deng G, Hauck W, Brown W, Manning R, Wahab S, 2007, Perturbation Study of Dissolution Apparatus Variables-A Design of Experiment Approach, *Dissolution Technologies*; 14(2): 20-26.

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collectively helped to identify sources of significant variability that are within the analyst's control. The published data show that dissolution variance within a lot of reference standard tablets can lead to the irreproducibility of dissolution measurements and contribute to uncertainty. Lack of sensitivity to variation and uncertainty hamper the ability of reference standard tablets to adequately calibrate dissolution apparatus.

The collective published findings and outcomes from these studies lead FDA to conclude that sole reliance upon reference standard tablets to evaluate the performance of USP Dissolution Apparatus 1 and 2 does not provide assurance that the apparatus is adequately calibrated as required by CGMP regulations in § 211.160(b)(4). Enhanced MC is advantageous, enabling a dissolution apparatus operator to minimize the significant sources of measurement system variation identified in the recently published studies.

We note that on August 1, 2007 (4th Interim Revision Announcement to USP 30), USP revised its General Chapter <711> *Dissolution* as follows: (1) removed the term *calibrator tablets* and replaced it with *reference standard tablets* to describe its Prednisone Tablets and Salicylic Acid Tablets and (2) retitled the <711> "Apparatus Suitability Test, Apparatus 1 and 2" to "Performance Verification Test, Apparatus 1 and 2." In explaining these changes to Chapter <711>, USP stated that "USP's RS tablets are not calibrator tablets – they are used in performance verification – and USP will no longer use the term *calibrator* to describe them."⁷ Subsequently, USP announced its intention as of December 1, 2009, to discontinue use of its Salicylic Acid Tablets RS (reference standard) in the Performance Verification Test for Dissolution Apparatus 1 and 2 in <711> (but it will retain its Prednisone Tablets RS).⁸

In October 2007, USP posted to its Web site a *toolkit* to provide laboratories with an MC procedure, aligning with mechanical tolerances in <711> for the dissolution apparatus assemblies.⁹ However, neither the mechanical tolerances specified in USP <711> nor the MC procedure described in the USP toolkit are as comprehensive or as stringent as those in the enhanced MC procedure recommended in this guidance.

III. RECOMMENDATIONS

We recommend that an appropriately enhanced procedure for MC can be applied to USP Dissolution Apparatus 1 and 2 as an alternative procedure to meet CGMP calibration requirements (§ 211.160(b)(4)). The calibration procedure should specify the frequency at

⁷ Deng G, Ashley AJ, Brown WE, Eaton JW, Hauck WW et al., 2008, The USP Performance Verification Test, Part I: USP Lot P Prednisone Tablets – Quality Attributes and Experimental Variables Contributing to Dissolution Variance, *Pharmaceutical Research*; 25(5): 1100-1109.

⁸ USP Proposes Changes to General Chapter <711> *Dissolution*, *Pharmacopeial Forum*; 34(5), September-October 2008: 1243-1251.

⁹ See USP Toolkit, Draft 5.1 October 2007, Section I. Mechanical Calibration, available on the Internet at <http://www.usp.org/pdf/EN/dissolutionProcedureToolkit2007-10-04.pdf>.

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which each calibration step is to be performed. Calibration schedules should take into account the potential for variation in each parameter known to be critical. An example of an appropriately enhanced MC procedure is that used by CDER/DPA titled *Mechanical Qualification of Dissolution Apparatus 1 and 2*, available on FDA's Web site at <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM142492.pdf>. This procedure describes the MC tolerances CDER/DPA uses in its laboratories to set up and maintain dissolution apparatus. Alternative methods of mechanical calibration can also be used to set up and maintain dissolution equipment, provided the chosen method is comparably enhanced to the FDA-recommended MC procedure so that mechanical variables that could significantly affect the accuracy and precision of test results are adequately controlled.¹⁰ Calibration procedures that rely solely on tests using reference standard tablets are generally not recommended, since they do not provide assurance that the apparatus is adequately calibrated, nor provide a reliable basis upon which to make precise tolerance adjustments to the dissolution apparatus.

Either the *Apparatus Suitability* procedure in <711> or an appropriately enhanced MC method executed according to a written procedure will satisfy the CGMP requirement for calibration of laboratory apparatus and mechanical equipment for manufacturing, as set forth in §§ 211.160(b)(4) and 211.68, respectively. For an approved drug product, the use of an alternative enhanced MC procedure instead of a performance verification test (e.g., USP <711> PVT) can be reported as a minor change in the applicant's next annual report, consistent with 21 CFR 314.70(d)(2)(vii).

In addition to performing enhanced MC or the *Apparatus Suitability* procedure, manufacturers also should take appropriate measures to control the following recognized sources of significant variability in dissolution testing.

1. Dissolved gases – Sometimes dissolved gases can cause bubbles to form around a dosage form undergoing testing, which can affect the results of a dissolution test.¹¹ To eliminate this source of variability, the dissolution medium is *degassed* or *deaerated*. The USP degassing procedure (vacuum filtration at 41°C, then cooling to 37°C before use) can be time-consuming, so some laboratories use an alternative technique such as vacuum degassing with agitation at ambient temperature.¹² Prednisone tablets are sometimes used as a reference standard to qualify the performance of these alternative degassing techniques. Instead, CDER/DPA uses a total dissolved gas pressure meter to accurately measure the amount of total dissolved gas in the medium. CDER/DPA recommends

¹⁰ See also ASTM E 2503-07, Standard Practice for Qualification of Basket and Paddle Dissolution Apparatus.

¹¹ Other factors that can influence dissolution results include (1) sampling probe size when automatic sampling is used; (2) method of tablet or capsule introduction into medium, including the use of sinkers (devices designed to make tablets or capsules sink to the bottom of the vessel); (3) basket construction (some vendors have *clips* to hold on the basket and others have o-rings); (4) vibration; and (5) accuracy of mechanical calibration procedures.

¹² Moore T, 1996, Dissolution testing: A Fast Efficient Procedure for Degassing Dissolution Medium, *Dissolution Technologies*; 3(2): 3-5.

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degassing to less than 60 percent saturation of total dissolved gases at room temperature.¹³

2. Vibration – There should be no significant vibration in the dissolution apparatus or medium. Some sources of vibration to guard against during apparatus installation and routine set up are:
 - the surrounding environment (HVAC, nearby equipment or operations)
 - the dissolution unit itself or one of its components
 - an external water bath circulating heater¹⁴
3. Vessel dimensions – Vessel symmetry and other dimensional attributes may affect dissolution performance. Vessels should conform to USP <711> criteria for dimensions and tolerances and should be examined routinely for any irregular shape or defects.¹⁵

¹³ Gao Z, Moore TW, Doub WH, Westenberger BJ, Buhse LF, 2006, Effects of Deaeration Methods on Dissolution Testing in Aqueous Media: A Study Using a Total Dissolved Gas Pressure Meter, *Journal of Pharmaceutical Science*; 95(7): 1606-1613.

¹⁴ For additional detailed information on vibration sources and recommended criteria, see USP Toolkit, Draft 5.1 October 2007, Section I. Mechanical Calibration, 1.2 Vibration, at <http://www.usp.org/pdf/EN/dissolutionProcedureToolkit2007-10-04.pdf>.

¹⁵ For a list of vessel attributes that might influence results, see USP Toolkit, Draft 5.1 October 2007, Section I. Mechanical Calibration, 2.5.3 Vessel, at <http://www.usp.org/pdf/EN/dissolutionProcedureToolkit2007-10-04.pdf>.