Guidance for Industry

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

DRAFT GUIDANCE

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

October 2007
Current Good Manufacturing Practices (CGMP)

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I. INTRODUCTION

This guidance is intended to aid drug manufacturers (including ancillary testing laboratories) in the use of mechanical calibration as an alternate approach to the use of calibrator tablets in calibrating an apparatus used for dissolution testing. This guidance provides references to information on critical tolerances that should be achieved with mechanical calibration.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidance documents describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance documents means that something is suggested or recommended, but not required.

II. BACKGROUND

FDA's CGMP regulations require that laboratory apparatus be calibrated at suitable intervals in accordance with established written specifications (21 CFR 211.160(b)(4)). Historically, both chemical and mechanical means have been used in calibrating dissolution apparatuses. Since 1978, chemical calibration has been the predominant method of calibration, consistent with Chapter 711 of the *United States Pharmacopeia* (USP), which describes the use of calibrator

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

tablets.[2] Chemical calibration of an apparatus is usually performed, in addition to mechanical calibration, every 6 months. Chemical calibration is also performed if a unit is moved or when there has been a major change made to the instrumentation.

In 1978, a 50-milligram (mg) prednisone tablet (manufactured by Upjohn) and a 300-mg salicylic acid tablet (manufactured by Hoffman LaRoche) became the official USP reference standards for the disintegrating and the non-disintegrating chemical calibration tablets, respectively. Before this time, laboratories solely relied on minimal mechanical calibration standards to make sure their apparatus was set up properly.

Over the years, a 10-mg prednisone tablet has become the official USP disintegrating chemical calibration tablet reference standard (RS). In 1979, CDER's Division of Pharmaceutical Analysis in St. Louis, MO (DPA), discovered a commercially available 10-mg prednisone tablet that was extremely sensitive to dissolved gases in the medium and vessel centering for the paddle method (Apparatus 2). CDER's DPA used this tablet as the in-house calibrator tablet for about 20 years. In 1997, Upjohn discontinued marketing its 50-mg prednisone tablet, which had been the USP disintegrating chemical calibration tablet RS for about 19 years. In 1999, USP replaced the 50-mg prednisone calibrator tablet (in use at that time) with a 10-mg prednisone tablet manufactured at the University of Maryland at Baltimore (UMAB) and similar in formulation to the in-house DPA calibrator tablet.

The use of USP calibration tablets can lead to variability in the dissolution measurement system. Unlike the original DPA 10-mg prednisone tablet, which is stable for over 20 years, the newer USP 10-mg tablet tends to give lower dissolution results with the paddle method and higher results with the basket method over time. Also, acceptance criteria for the prednisone tablet RS (10 mg) are based on a collaborative study and tend to cover a wide range to accommodate data from multiple laboratories (original ranges of 27 to 48 percent for lot O0C056 for Apparatus 2 and 53 to 77 percent for Apparatus 1). Because of stability problems, in December 2004, USP officially changed the limits for this lot to 26 to 47 percent for Apparatus 2 and 51 to 81 percent for Apparatus 1.[3] The newest lot (P0E203) also has wide ranges: 37 to 70 percent for Apparatus 2 and 47 to 82 percent for Apparatus 1. Further, a collaborative study by DPA and the Pharmaceutical Research and Manufacturers of America (PhRMA) has found that the USP Salicylic Acid Tablet is operationally insensitive to perturbations of both USP Apparatus 1 and 2.[4]

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[2] The United States Pharmacopeial Convention, *United States Pharmacopeia 30– National Formulary 25* (2007). The specific method to be used for chemical calibration of dissolution equipment is not in Chapter 711 of the USP. When a bottle of USP calibrator tablets is purchased, the USP sends a sheet that contains the instructions on how to run the test and the acceptance criteria.

[3] See USP Official Dissolution Calibrator Ranges, available on the Internet at http://www.usp.org/referenceStandards/useAndStorage/calibrators.html.

[4] 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.

There can also be other sources of variability in the dissolution measurement system. For example, sometimes dissolved gases can cause bubbles to form around a dosage form undergoing testing, which can affect the results of a dissolution test.[5] To eliminate this source of variability, the dissolution medium is degassed. 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.[6] The calibrator tablets are sometimes used to ensure sameness between the alternative technique and the USP method for degassing. DPA uses a total dissolved gas meter to accurately measure the amount of total dissolved gas in the medium to ensure adequate degassing.[7]

Because variability of the USP chemical calibration tablets makes it difficult to assess the calibration of dissolution equipment, FDA is providing guidance on mechanical calibration as an alternate approach to calibrating dissolution equipment.

III. RECOMMENDATIONS

Instead of using a calibrator tablet, a firm can use an appropriately rigorous method of mechanical calibration for dissolution Apparatus 1 and 2. An example of an appropriately rigorous mechanical calibration procedure is used by CDER's DPA and is titled *Mechanical Qualification of Dissolution Apparatus 1 and 2*, available on FDA's Web site at http://www.fda.gov/cder/Offices/OTR/default.htm. This procedure describes the mechanical calibration tolerances DPA uses in its laboratories to set up and maintain dissolution apparatuses. Alternatively, a firm can choose another method of mechanical calibration—instead of calibrator tablets—to set up and maintain dissolution equipment, provided the method is sufficiently rigorous.[8]

A compendial product would still need to meet the dissolution requirements for its USP monograph whether mechanical calibration or the USP calibrator tablet approach is used (section 501(b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351(b)). We believe that this change in calibration methodology, from the use of tablets to rigorous mechanical calibration, will reduce the bias and variation in the measurement system and therefore is an appropriate alternative approach. An appropriately rigorous mechanical calibration method properly

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[5] 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.

[6] Moore T, 1996, Dissolution testing: A Fast Efficient Procedure for Degassing Dissolution Medium, Dissolution Technologies, 3(2):3-5.

[7] 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.

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

executed will satisfy the CGMP requirement for dissolution apparatus calibration under § 211.160(b)(4).