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FIP Position Paper on Qualification of Paddle and Basket Dissolution Apparatus

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ABSTRACT

The qualification process for ensuring that a paddle or basket apparatus is suitable for its intended use is a highly debated and controversial topic. Different instrument qualification and suitability methods have been proposed by the pharmacopeias and regulatory bodies. In an effort to internationally harmonize dissolution apparatus suitability requirements, the International Pharmaceutical Federation's (FIP) Dissolution/Drug Release Special Interest Group (SIG) reviewed current instrument suitability requirements listed in the United States, European, and Japanese pharmacopeias and the International Conference on Harmonization (ICH) Topic Q4B on harmonization of pharmacopoeial methods in its Annex 7, Dissolution Test General. In addition, the SIG reviewed the Food and Drug Administration (FDA) Draft Guidance for Industry, "The Use of Mechanical Calibration of Dissolution Apparatus 1 and 2—Current Good Manufacturing Practice (CGMP)" and the related ASTM Standard E2503-07. Based on this review and several in-depth discussions, the FIP Dissolution/Drug Release SIG recommends that the qualification of a dissolution test instrument should be performed following the calibration requirements as indicated in the FDA (draft) guidance. If additional system performance information is desired, a performance verification test using U.S. Pharmacopeia Reference Standard tablets or an established in-house reference product can be conducted. Any strict requirement on the use of a specific performance verification test tablet is not recommended at this time.

INTRODUCTION

Over the last four decades, the dissolution test has evolved into a powerful method for characterizing oral drug products. It is an important tool for assessing lot-to-lot quality of a drug product, guiding development of new formulations, and ensuring continued product quality and performance after post-approval changes in formulation, manufacturing process, site of manufacture, and scale-up of the manufacturing process. This has been possible only because of our increased knowledge and understanding of the science behind dissolution test methodology and continuous improvement of the instrumentation.

The engineering of dissolution testing instruments has evolved over the years. This has resulted in the availability of precise, rugged, and reliable dissolution apparatus. Because dissolution is not an absolute method, no definitive standard is available against which to verify the performance of the apparatus. Thus, qualification of dissolution instruments needs to include a complete description of the instrument dimensions and setup to ensure meaningful dissolution results.

Currently, the qualification process for ensuring that a paddle or basket apparatus is suitable for its intended use is a highly debated and controversial topic. Different instrument qualification and suitability methods have been proposed by various pharmacopeias and regulatory bodies. For example, chapter 711 of the *United States Pharmacopeia* (USP) describes mechanical calibration specifications and the use of performance verification reference tablets, historically known as calibrator tablets, to establish instrument suitability (*1*). The Food and Drug Administration (FDA) has issued a draft guidance for

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industry, "The Use of Mechanical Calibration of Dissolution Apparatus 1 and 2—Current Good Manufacturing Practice (CGMP)," recommending that a properly executed rigorous mechanical calibration will satisfy CGMP requirements for dissolution apparatus calibration in lieu of performance verification with specified tablets (*2*). The *European Pharmacopoeia* (Ph. Eur.) recommends mechanical calibration for instrument qualification and suggests that the performance of the dissolution test instrument may be monitored by the selection and testing of an appropriate reference product (*3*). The *Japanese Pharmacopoeia* states that the fundamental system suitability of the dissolution apparatus must include conformance to the dimensions and tolerances stated in chapter 6.10 Dissolution Test, but specific requirements on performance verification of the apparatus are not given (*4*). Hence, the International Conference on Harmonization (ICH) Topic Q4B on harmonization of pharmacopoeial methods, in its Annex 7, Dissolution Test General Chapter, notes that the harmonized dissolution test apparatus should be calibrated to ensure compliance with regional good manufacturing practice (GMP) requirements (*5*).

This article offers a review of the current instrument qualification proposals and provides recommendations from the International Pharmaceutical Federation's (FIP) Dissolution/Drug Release Special Interest Group (SIG) on how to ensure that the dissolution apparatus is appropriately qualified for its intended use.

HISTORY/BACKGROUND

A significant step towards standardizing the dissolution methods and resolving lab-to-lab result discrepancies occurred in the 1980s (*6*). The specifications and acceptance criteria for the USP calibrator tablets (prednisone and salicylic acid) were established from collaborative study results organized by the Pharmaceutical Manufacturer's Association (PMA)/ Pharmaceutical Research and Manufacturers of America (PhRMA). The dissolution values from six individual units had to comply with an established range for %-dissolution to qualify the instrument for routine operation (*7*). Originally, calibrator tablets were adopted to detect the influence on dissolution results due to improper alignment of the instrument, vibration in the instrument, failures in the drive chains and belts, and deaeration (*8*). Thus, the calibrator tablet became an important check on operating procedures, especially in terms of consistency between laboratories on an international basis (*9*). The testing with USP calibrator tablets is currently described in USP 711 as the Performance Verification Test. The precise engineering of dissolution instrumentation and the ability to accurately measure the instrument's mechanical operations has caused the industry to question the USP's performance verification requirement utilizing the historical calibrator tablet practice.

In 2000, PhRMA published results from a collaborative study to evaluate the performance of the then current USP 50-mg prednisone and 300-mg salicylic acid* reference tablets and a 10-mg prednisone tablet from the FDA Division of Pharmaceutical Analysis (DPA) known as NCDA#2 (*8*). Their recommendations included enhanced mechanical calibration testing on each dissolution bath and a reduction in reliance on the testing of USP reference standard (calibrator) tablets. This approach was endorsed by the FDA Pharmaceutical Science Advisory Committee in October 2005 (*9*). The American Society for Testing and Materials (ASTM), a voluntary consensus standard-setting organization, created a standard for mechanical calibration of basket and paddle dissolution apparatus building on these recommendations (*10*).

CURRENT INSTRUMENT QUALIFICATION PROPOSALS

According to USP 32–NF 27 2009, the suitability of the dissolution paddle or basket assembly is determined by conformance to the dimensions and tolerances stated in its Chapter 711. Dissolution medium volume, temperature, and shaft rotation speed need to be monitored during use. In addition, the USP requires a performance verification test with reference standard tablets, formerly called calibrator tablets. For Apparatus 1 and 2, disintegrating prednisone reference standard tablets are used to establish system suitability.

FDA's CGMP regulations require that laboratory apparatus are calibrated at suitable intervals according to established written procedures and specifications (*6*). Recently, the FDA issued a draft guidance for industry, The Mechanical Calibration of Dissolution Apparatus 1 and 2—Current Good Manufacturing Practice (CGMP). The draft guidance recommends a more rigorous mechanical calibration of the paddle and basket apparatus as a suitable alternative to the USP Performance Verification Test (PVT). In the spirit of continuous improvement, this change in qualification procedure has been proposed since the wide acceptance range of the Performance Verification Test results makes it difficult to assess the suitability of the dissolution apparatus.

ASTM Standard E2503-07 (*10*) provides guidance for basket and paddle dissolution apparatus setup and calibration to ensure reproducibility of results without specifying how to perform dissolution testing. This standard takes a more detailed approach to instrument setup than is currently outlined in the harmonized pharmacopeial chapters by providing quantitative criteria for shaft wobble. Shaft and vessel verticality are new parameters not currently addressed in the pharmacopeial chapters. The ASTM standard also has tighter criteria for shaft/vessel centering (vessel offset), rotational speed, and basket wobble than that given in the Pharmacopoeial Discussion Group (PDG) harmonized dissolution test. This

**The requirement for use of the salicylic acid tablets will be eliminated at the end of calendar year 2009.*

change in calibration methodology, from the reliance on less stringent methodology and use of tablets to rigorous mechanical calibration, will reduce the bias and variation in measurement systems. Hence, FDA states that properly executed rigorous mechanical calibration will satisfy the CGMP requirements for dissolution apparatus calibration in lieu of chemical tablet calibration.

Ideally, knowledge of how the product is affected by each source of instrument-related variability will allow tighter control of those variables and result in more meaningful decision making from any dissolution data that are generated. In the absence of such knowledge, rigorous mechanical setup criteria will ensure less instrument contribution to test-method variability.

The *European Pharmacopoeia* (*3*) recommends that the qualification of the dissolution test instrument has to consider the dimensions and tolerances specified for the apparatus. Parameters such as dissolution medium temperature and volume, rotation speed, and sampling probes need to be monitored periodically during use. The following general statement is made in reference to a performance test: "The performance of the apparatus may be monitored by testing a reference product that is sensitive to the hydrodynamic conditions. Such tests may be performed periodically or continuously for comparative reason with other laboratories (*3*)." Based on this Ph. Eur. recommendation, individual laboratories can independently determine if a reference product test is needed, and if so, the laboratories are responsible for the selection and qualification of an appropriate reference product for performance verification.

The *Japanese Pharmacopoeia* (*4*) states that the fundamental system suitability of the dissolution apparatus must include conformance to the dimensions and tolerances stated in chapter 6.10 Dissolution Test. In addition, critical test parameters, such as rotation speed and volume and temperature of the dissolution medium, must be monitored periodically during use. The JP also states that apparatus performance should be monitored periodically, but specific requirements on performance verification of the apparatus are not given.

For comparison, Tables 1 and 2 detail the harmonized PDG and FDA mechanical calibration requirements for basket and paddle apparatus, respectively.

In 1997, the FIP Dissolution Working Group issued a guideline on the Dissolution Testing of Solid Oral Products (*11*). In the guideline, FIP states that dissolution apparatus qualification should include conformance to the geometrical and dimensional specifications and verification of operational parameters such as test medium, temperature and volume, and rotation speed during periods of use. FIP acknowledged that apparatus suitability testing is an important aspect of qualification, and while the USP calibrator tablets were acknowledged to be controversial at that time, the FIP still supported the use of these calibrators since they were the only standards available and had been helpful in identifying system and operator failures. In the same guidelines,

Table 1. Mechanical Calibration Parameters: Dissolution Rotating Basket Apparatus

Calibration Parameter	PDG harmonized pharmacopeial specifications (USP, EP, JP)	FDA recommendations based on ASTM standard
Shaft wobble	Rotates smoothly without significant wobble	≤1.0 mm total runout
Shaft verticality	N/A	Bubble must be within the lines of bubble level (≤0.5° from vertical)
Basket wobble	±1 mm runout	≤1.0 mm total runout
Vessel/shaft centering	≤2.0 mm from centerline	≤1.0 mm from centerline measured at an upper and lower position
Vessel verticality	N/A	≤1.0° from vertical
Height check/ basket depth	25 ± 2 mm	25 ± 2 mm
Rotational speed	±4% from target	±2 rpm from target

FIP also proposed that since some drug products might reveal similar or even higher sensitivity to apparatus variability than the USP calibrator tablets, "in-house" standards were considered to be an acceptable alternative to the USP calibrator tablet.

NEW FIP INSTRUMENT QUALIFICATION RECOMMENDATION

In the spirit of continuous improvement, the FIP SIG on Dissolution/Drug Release supports the more stringent

Table 2. Mechanical Calibration Parameters: Dissolution Rotating Paddle Apparatus

Calibration Parameter	PDG harmonized pharmacopeial specifications (USP, EP, JP)	FDA recommendations based on ASTM standard
Shaft wobble	Rotates smoothly without significant wobble	≤1.0 mm total runout
Shaft verticality	N/A	Bubble must be within the lines of bubble level (≤0.5° from vertical)
Vessel/shaft centering	≤2.0 mm from centerline	≤1.0 mm from centerline measured at an upper and lower position
Vessel verticality	N/A	≤1.0° from vertical
Height check/ paddle depth	25 ± 2 mm	25 ± 2 mm
Rotational speed	±4% from target	±2 rpm from target

mechanical calibration approach. In an effort to internationally harmonize dissolution apparatus suitability requirements, the need and type of performance verification tests should be determined by the individual laboratories based on the type of testing they are performing. Any strict requirement on the use of a specific performance verification test tablet is not recommended at this time.

Any product established as an in-house performance verification reference product should be well characterized , sensitive to critical parameters of the dissolution test such as different hydrodynamic conditions, and representative of the products currently being tested in that laboratory. For most marketed products, extensive dissolution studies are conducted during product development, method validation, and laboratory-to-laboratory method transfers prior to final approval of the product. Analysis of method development, transfer, and validation data, as well as registration stability data, can insure confidence in the characterization of the in-house performance verification product and facilitate the establishment of acceptance criteria. The recommended acceptance criteria should include mean value, standard deviation, and stability. Gauge repeatability and reproducibility studies can be useful for determining the mean and variability of a dosage form and for improving equipment variability (*12*). If different from the product(s) to be tested, a reference product should be sensitive to the same variables that affect the products tested in that laboratory.

The FIP recommends that the qualification of a dissolution test instrument should be performed following the calibration requirements as indicated in the FDA (draft) guidance. If additional system performance information is desired, a performance verification test using USP reference standard tablets or an established in-house reference product can be conducted.

In the future, improvements in instrument technology, performance verification standards, and the ability to measure hydrodynamic variables may change this recommendation.

CONCLUSIONS

The dissolution test procedure is well established, reliable, and reproducible, and it is a valuable tool for characterizing a drug product at different stages in its lifecycle. A thorough understanding of all sources of variability within dissolution laboratory systems will minimize uncertainty when examining or acting on results. Qualification of the dissolution system should include verification of the dimensions and tolerances of the apparatus. Critical test parameters such as rotation speed, media temperature, and volume need to be monitored periodically during use. Overall system performance can be monitored by running a performance verification test by testing a well-characterized dosage form, such as USP performance verification tablets or an in-house product, with sufficient knowledge of the mean, variability, and stability. As a standard practice, laboratory scientists are encouraged to critically evaluate dissolution data variability within and between laboratories to determine if the variability is product-related versus laboratory system-related.

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