dx.doi.org/10.14227/DT180211P6

Overview of Dissolution Instrument Qualification, Including Common Pitfalls

e-mail: greg.martin@complectors.com

Gregory P. Martin[1,*] and Vivian A. Gray[2]

[1]*Complectors Consulting LLC, Pottstown, PA 19465*

[2]*V. A. Gray Consulting, Hockessin, DE 19707*

INTRODUCTION

For almost fifty years, the pharmaceutical community has been relying on dissolution data as an indication of drug product performance (*1*). Effective qualification of the dissolution apparatus is critical to the value and integrity of these data.

Qualification of dissolution instruments has always been challenging. Apparatus performance can be influenced by variability in several mechanical parameters. Data are affected by the physical and chemical properties of the drug product. Dissolution performance is also changing rapidly while the samples are collected. Recently there have been several significant changes in regulatory and compendial guidances related to the qualification of these instruments. For these reasons, it is imperative that scientists who generate dissolution data understand the challenges associated with qualification of dissolution apparatus, become aware of the recent changes, and address them in their organizations.

BASIS FOR INSTRUMENT QUALIFICATION REQUIREMENTS

Calibration and qualification of equipment are key requirements in the GMP guidelines of the FDA and the EU. In the United States, this is specified in 21CFR 211.160, under Subpart I: Laboratory Controls. The *United States Pharmacopeia* (*USP*) includes a general chapter, <1058> Analytical Instrument Qualification, which describes the overarching approach to instrument qualification. There is additional detail in *USP* General Chapter <711> Dissolution, which is representative of globally harmonized text for dissolution and indicates, "the suitability for the individual apparatus is demonstrated by the Performance Verification Test."

DISSOLUTION APPARATUS QUALIFICATION

Qualification is more challenging for the dissolution apparatus than for most instruments, because there are physical, chemical, and temporal factors that can affect the results. Several factors that have been identified as important are the physical dimensions of the apparatus and its components, vibration resulting from the apparatus itself or from nearby equipment, temperature control, solubility of the drug being dissolved, hydrodynamics in the vessel, vessel geometry, sampling and filtering effects (including timing of these activities), and deaeration of the medium (*2*, *3*). There are several mechanical measurements that can be made to demonstrate conformance to the compendial requirements, such as those listed in *USP* <711> Dissolution (*4*). There are mechanical specifications for:

1. The vessel including height and inside diameter requirements and a hemispherical bottom.
2. The stirring units (i.e., dimensions for the basket or paddle and for the wire mesh of the baskets).
3. The assembled unit (wobble and runout for the shafts, distance between the vessel and the bottom of the basket or paddle, rotation speed, and temperature of the medium).

Furthermore, there is a requirement for "no significant motion, agitation, or vibration beyond that due to the smoothly rotating stirring element."

Additional considerations include training of analysts, qualification of spectrophotometers used for the determinative step, and verification of the *USP* procedure in the laboratory including filter qualification and effectiveness of deaeration.

Since the late 1970s, the USP has provided reference tablets that allow a holistic evaluation of the apparatus. Prednisone Tablets RS are currently used for the performance verification test (PVT) for USP Apparatus 1 (basket) and Apparatus 2 (paddle). USP provides specifications based on a collaborative study from multiple laboratories. This approach incorporates variability from all the factors listed above into the acceptance criteria. Use of these tablets has allowed comparison of results for the same lot of tablets among apparatus, analysts, and laboratories.

ISSUES WITH THE USP PERFORMANCE VERIFICATION TEST

Historically, there have been many concerns with the USP Performance Verification Test, or the Calibrator Tablets, as they were previously identified (*5*–*8*). First, the range of the acceptance criteria has been relatively wide compared with other compendial tests. This is the result, at least in part, of attempting to collect samples during a time of rapid change in the amount dissolved in the dissolution medium. Despite this, failures in the laboratory occur. It has often been difficult to identify the cause of the failure,

**Corresponding author.*

and many laboratories have noted that if the test is rerun, the results will pass. This led to studies that investigated the sources of variability in the dissolution results. A PhRMA perturbation study published in *PF* in 2000 (*9*) showed sensitivity of the NCDA2 tablets (similar to the current prednisone reference tablets) to centering, vibration, wobble, and shaft verticality. Other studies have shown that vibration, deaeration, sampling techniques, and vessel geometry can influence test results (*10–13*).

VERIFICATION OF THE ANALYTICAL PROCEDURE

Integral to the PVT is the analytical procedure for measuring samples. As with all *USP* procedures, this must be verified by the laboratory performing the procedure. Verification, described in *USP* <1226> Verification of Compendial Procedures, should address accuracy, precision, linearity, range, and filter qualification. Since some details are not listed in the *USP* procedure, they should be documented by the laboratory. These include the preparation of the standard and sample solutions including filters used, discard volume, and deaeration technique.

RECENT CHANGES IN THE REQUIREMENTS FOR DISSOLUTION APPARATUS QUALIFICATION

During the last several years, there has been a significant amount of activity related to dissolution apparatus qualification, resulting in significantly revised requirements from both the FDA and USP (*14–17*). In addition, an FIP Position Paper that recommends mechanical qualification (*18*) was published. These changes encompass the measurements or tests that must be performed and the evaluation of data from dissolution testing of reference tablets.

FDA has recently issued a guidance document on dissolution apparatus qualification. Guidance for Industry: *The Use of Mechanical Calibration of Dissolution Apparatus 1 and 2—Current Good Manufacturing Practice* was issued in January 2010 (*17*) following a draft issued in October 2007. This guidance calls for "enhanced mechanical calibration," which is more comprehensive and stringent than the requirements specified in *USP* <711> Dissolution. The Guidance states that FDA and USP laboratories have identified several different sources of variation within Apparatus 1 and 2 that can be minimized by employing the enhanced mechanical calibration procedure. They recommend "either the Apparatus Suitability Test in <711> or an appropriately enhanced mechanical calibration method executed according to a written procedure will satisfy the CGMP requirement for calibration of laboratory apparatus."

A comparison of the FDA Mechanical Qualification specifications and those from the USP Dissolution Toolkit is shown in Table 1. Note that both documents identify the need to conform to the specifications described in *USP* <711> Dissolution. The USP Dissolution Toolkit also includes specifications for base plate level (not more than 0.5° in two orthogonal directions), volume (+1%), and timing for sampling and filtration (+2% or 36 sec for 30-min samples), which are not mentioned in the FDA Mechanical Qualification document.

Table 1. Comparison of Dissolution Mechanical Calibration Specifications

Calibration Parameter	FDA Mechanical Calibration Specifications *(16)*	USP Dissolution Toolkit Specifications *(20)*
Shaft Wobble	≤1.0 mm runout, 2 cm above the paddle or basket	≤1.0 mm runout, 1 cm above the paddle or basket
Shaft Verticality	<0.5° from vertical at 2 points 90° apart	<0.5° from vertical at 2 points 90° apart
Basket Wobble	≤1.0 mm runout at bottom of basket	≤1.0 mm runout at bottom of basket
Centering	≤1.0 mm, at 2 mm and 60 mm above basket or at 2 mm and 80 mm above paddle	≤2.0 mm, not more than 2 cm below the flange of the vessel
Vessel Verticality	<1.0° from vertical at 2 points 90° apart	<0.5° from vertical at 2 points 90° apart
Height of basket or paddle, above bottom of vessel	25 ± 2 mm	25 ± 2 mm
Rotational Speed (50 rpm)	±2 rpm	±1 rpm
Temperature	37 ± 0.5 °C	37 ± 0.5 °C, range not more than 0.4 °C

During the same period, USP was actively working on dissolution apparatus qualification and introduced several significant changes (*14*, *15*, *19*). These included discontinuation of the use of salicylic acid tablets as part of the Performance Verification Test and changes to the PVT accept–reject decision from one based on per-tablet results to one based on the mean and CV for the set of results. USP introduced the use of geometric mean, stating elsewhere that it improved the normality assumption and allowed the use of a two-stage test. USP also introduced a Dissolution Toolkit: Procedures for Mechanical Calibration and Performance Verification Test (*20*), which includes much more detail than <711> Dissolution.

OUTSTANDING ISSUES

Despite the recent changes by FDA and USP, some issues remain. Vibration is recognized as a parameter that can have a significant effect on dissolution results, but there is still no generally accepted procedure for measuring vibration, nor are there associated acceptance criteria. USP Prednisone Tablets RS for PVT are sensitive to vibration effects (*10, 13, 21*). A second issue arises with vessel geometry. While it is recognized that there are

several aspects of vessel geometry that can impact dissolution results (such as the spherical shape of the vessel bottom, perpendicularity of the vessel axis to the plane of the flange, variations in flange thickness), there are no readily available and effective tests for measuring these parameters (*22*, *23*). The USP Prednisone Tablets RS for PVT have also shown dissolution rate and variability differences among vessel manufacturers (*24*).

RESPONSE OF INDUSTRY

After years of struggling with the issues related to dissolution apparatus qualification, industry may be ready for some changes. In an October 2010 survey of its members (*25*), the AAPS In Vitro Release and Dissolution Testing Focus Group (IVRDT FG) found that the majority of respondents were still following the USP PVT, but about 25% had adopted the procedures in the FDA Draft Guidance on Enhanced Mechanical Calibration, and a similar percentage plan to switch to the FDA procedure. In the meantime, some laboratories have adopted a hybrid of the two, implementing whichever mechanical criteria are stricter, while continuing to perform the USP PVT either routinely or when an instrument is new or has a significant change.

The change in *USP* acceptance criteria from individual vessels to the mean and CV should result in few failures for the PVT, but almost half of the respondents reported PVT failures. The assignable cause identified most frequently was deaeration.

IMPLICATIONS FOR COMPLIANCE

Dissolution data are an important factor for demonstrating formulation performance. Because of the importance of these data, dissolution instruments must be well qualified to support the data generated on those instruments. Dissolution instrument qualification data are frequently scrutinized during regulatory inspections. Instruments that are not qualified and requalified in a timely manner can raise questions about the validity of the dissolution data generated for a drug product.

GENERAL EXPECTATIONS

General expectations based on industry practices and detailed in the FDA Mechanical Qualification document (*16*) include qualification (1) at installation, (2) whenever an instrument is moved or has another significant change, and (3) every six months. If the instrument is used only for baskets or paddles, it need only be qualified for that particular apparatus. If an instrument is used very infrequently, periodic requalification can extend for periods longer than six months as long as the apparatus is requalified before use.

PERFORMANCE VERIFICATION TEST (PVT)

With the introduction of options such as the Performance Verification Test or the Enhanced Mechanical Calibration, it is important to document which approach is adopted by your laboratory, including detailed procedures and acceptance criteria (*25*). If the *USP* Performance Verification Test is used, this procedure must be verified as described above.

One aspect of standard operating procedures that should be clearly specified is the timing of periodic Performance Qualification. Most laboratories choose a fixed interval, such as six months, for requalification, but it is not always convenient to requalify on the day it is due. Some laboratories have adopted a practice that an instrument may continue to be used beyond the requalification date, perhaps until the end of the month or for an additional 30 days. If your laboratory adopts a practice such as this, be sure to document it carefully to avoid the appearance of noncompliance for an apparatus that is a few days beyond its requalification date.

Who Should Do the PVT?

Because of the unusually complex nature of the dissolution instrument, appropriate training of those performing the qualification is crucial. It is sometimes tempting to assign this task to the newest member of the staff. Be aware of the implications of generating failing data for a dissolution qualification test; it has the potential to call into question all data generated on that instrument since the previous qualification. For this reason, a more appropriate approach might be to assign the qualification testing to seasoned personnel and to use a repeat of the qualification testing as a proficiency requirement in the training of new personnel.

Evaluation of Failing PVT Data

As mentioned, failing data for a dissolution qualification test can have profound effects on the validity of drug product data that were generated on that instrument since the prior qualification. For this reason, it is wise to address this in your standard operating procedure. No one wants to invalidate six months of dissolution data, but failing data for a requalification demands an investigation. The investigation may show that the assignable cause is due to the qualification testing rather than the instrument, but sometimes no clear cause can be assigned. In this situation, it may be possible to use inferential data to show that laboratory results for products were valid (for instance, if stability data were comparable to initial data), but it is better from a compliance perspective to document in your SOP the approaches that will be used in the event of a requalification failure.

Causes of Failing PVT

Failing results obtained during dissolution instrument qualification are not rare, especially when the Performance Verification Test is performed. An awareness of some of the most frequent causes can aid in your investigation (*5–8, 11–13*). In our experience, some of the most frequent causes are deaeration of the medium, vessel geometry, vibration, and sampling procedures, which are described

below. If failing results are observed, it is important to have a plan for investigation with a goal of identifying and correcting the cause. *USP* allows second-stage testing; any testing beyond that should be part of a well-planned and documented investigation.

Medium Deaeration

USP describes a deaeration procedure, but many laboratories use alternate procedures. It may be important to evaluate the effectiveness of the deaeration procedure in the vessel at the time of the test. Different levels may result from the native level of dissolved gases, the extent to which gases are removed during deaeration, and the reintroduction of air to the medium (either by pouring operations or while the apparatus is stirring before the start of the test). Techniques for measuring effectiveness by monitoring either dissolved oxygen or total gases have been described elsewhere (*26*, *27*).

Vessel Geometry

Vessel geometry is difficult to verify empirically in the laboratory. Perhaps the best approach to assure conformance is to purchase vessels from a reputable supplier.

Vibration

For many years, vibration has been a concern of those performing dissolution testing. Tales abound regarding dissolution results that were affected by a centrifuge on the same bench, or by construction adjacent to the laboratory. No consensus has been reached regarding metrological determination of vibration, and many laboratories rely on the sense of touch (a finger on the lip of the dissolution vessel) to detect unwanted vibration. The top plates should be examined so there is no sagging. The spindle assembly should be manually turned and felt for resistance.

Sampling

Sampling errors can be introduced in several ways. Filters used to clarify the sample must be qualified, and this often requires that a certain volume of medium be discarded before collecting the sample. Timing of samples is restricted to ±2% or 36 sec for the PVT. If automated equipment is used for sampling, verification that it will produce equivalent results is necessary.

CONCLUSIONS

Qualification of dissolution instruments is important and necessary because of the importance of dissolution data in demonstrating drug product performance and the requirements established by the FDA, USP, and other regulatory agencies. Qualification of these instruments is also challenging because of the large numbers of parameters that must be controlled and the dynamic nature of the test. While most practitioners in the industry can agree on many of the parameters that are critical, this has been and continues to be an area of controversy. At the current time, recommendations from FDA and USP are not in complete agreement with one another regarding dissolution instrument qualification procedures. Even beyond these recommendations, there are issues such as vibration and vessel geometry that have not yet been effectively addressed.

Each laboratory that is using dissolution instruments to generate data should be aware of the issues and decide proactively how they will be addressed in appropriate standard operating procedures. This may include adoption of the FDA recommendations, those from the *USP*, or a combination of both. Timing and other reasons for requalification should be addressed. The analytical procedures should be carefully documented. If the USP analytical procedure is used, it should be appropriately verified. The procedures should be executed by well-trained personnel. The SOPs should also identify a plan for the investigation of failing results for dissolution instrument qualification or requalification.

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