

USP Performance Verification Testing Recommendations and Troubleshooting for Lot P1I300

White Paper

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Introduction

The United States Pharmacopeia (USP) Performance Verification
Test (PVT) acceptance criteria were significantly altered with the new lot of prednisone tablets, P1I300, released on March 1, 2010. This lot of tablets, which is a continuation of lot P0E203 (1), has different acceptance criteria than previous lots, as well as minor modifications to the recommended testing criteria.

The new lot of prednisone PVT tablets has a number of major changes from the previous lots, including the following criteria:

- the change in approach from single tablets meeting the geometric mean within a specific range
- addition of a %CV component
- options for single and dual-stage testing
- testing based on a set of n=12 to n=16 tablets.

The USP re-evaluated the lot of tablets under a new collaborative study with the intent of moving away from the previous practice of a per tablet approach for acceptance, and moving toward a more holistic view of the dissolution apparatus. (2)

The new acceptance criteria and protocol have generated a great deal

of skepticism in the pharmaceutical industry, and the failure rate appears to be at a much higher level than the previous lots, primarily in meeting the %CV criteria for paddles. Given that the tablets are from the same lot as the previous one, this has also added to confusion.

The new specifications are intended to find and correct for variability of the dissolution apparatus, which the previous range was not able to do. Variability can come from a number of sources including the dissolution apparatus, the apparatus' accessories, the analyst and laboratory environment. It can be difficult to determine which of these factors play a role in a failing run, and after a failure, all of these variables should be evaluated for potential impact to the dissolution test.

PVT Calculations Overview

Whole assembly geometric mean versus individual position (per tablet) approach

The geometric mean for the entire test is now used in place of per tablet results to determine pass/fail against a range. A failure no longer results if one or more tablet values are outside of the range specified as long as the geometric mean is within the range.



%CV addition

The %CV criteria appear to be the most challenging to meet with the new specifications. This approach looks at the variability of the dissolution test itself in order to identify potential issues with the apparatus and allows for reproducible test conditions.

Single- and Dual-stage Testing Options

Each laboratory now has the choice of implementing either a single- or dual-stage testing scheme. The dualstage option allows the laboratory to perform one run of six to eight individual tests on an apparatus. If this meets the tighter criteria for a single set of data, the apparatus is considered qualified and a second test is unnecessary. If the first test does not meet these criteria, a second stage is performed and the geometric mean and %CV for the combined data of both runs would be evaluated versus the second stage range. If a problem is noted with the dissolution apparatus at the end of the first stage, a second run is unnecessary. Once the necessary changes are made to this apparatus, testing would restart again at the first stage (3). Also, if the first stage does not meet the required criteria, this is not considered a failure. A failure only occurs after both stages have been tested and have not met the criteria.

In the single-stage test, the laboratory would perform 12 to 16 individual tests, or typically two dissolution tests, and evaluate the total set of data as with the second stage of the two-stage test. Each laboratory must determine whether to adopt the single- or dual-stage testing prior to performing the PVT (3), and this should be defined within the laboratory's SOPs.

The calculations themselves are more fully explained within the USP PVT Lot

P1I300 certificate (4) and an online calculation tool (5). It should be noted that the online calculation tool is not validated and should be used as a crosscheck of internal calculations.

Perspective on Mechanical Calibration

Given that the new specifications are focused on the variability of the dissolution test, close attention should be paid to the dissolution apparatus, accessories, procedure and the laboratory environment prior to the start of a test. Specifications outlined in USP <711> must be followed, and in respect to elements such as centering and basket run out, it is prudent to reduce sources of variability by following the stricter guidance found in the USP Toolkit 2.0 or mechanical calibration documents such as the FDA and ASTM.

Dissolution Apparatus Mechanical Specifications

The dissolution apparatus must comply with USP< 711> mechanical criteria. Some specific areas of concern regarding the PVT test beyond the previous criteria include vibration, centering, and vessel verticality.

Vibration

Vibration is a poorly understood element in dissolution, but does impact the dissolution apparatus and generally leads to higher and more variable results. Vibration should be controlled as much as possible, and it can come from either the dissolution apparatus or the laboratory environment.

Vibration originating within the dissolution apparatus may come from several sources such as worn/loose belts or spindles in poor condition. Belts should be replaced if they appear worn or if there is excess material in the head of the apparatus.

Belt tension can also be adjusted and can reduce vibration. Chuck head spindles can also be a source of vibration if the internal ball bearings are rusty or significantly worn.

Vibration from either of these sources can be measured with a vibration meter or can be felt by placing a couple of fingers gently on the underside of the apparatus head while it is running.

The heater/circulator can also be a source of vibration, though it should be kept separate from the dissolution apparatus (i.e. not in direct contact). Typically, the heater/circulator only contributes to vibration if it is in direct contact or is in need of repair. Testing vibration by gently touching the unit should be sufficient to determine if there is an issue. In addition to the circulator being in good repair, it is also recommended to maintain an adequate water level in the water bath. This ensures the input flow from the circulator does not splash and is gently flowing into the bath. A baffle can also be used at this input to reduce and disperse the force of the flow so that it does not disturb the vessels.

The dissolution environment can also introduce vibration to the dissolution apparatus. The apparatus should be placed onto a sturdy bench top that can support at least 200 lbs. The apparatus should not be located on the same table with other equipment which may induce vibration, including but not limited to shakers, sonicators, centrifuges, vacuum pumps, tapped density testers, etc. At times, the larger laboratory environment may also be a source of vibration with the potential of heavy foot traffic, sharing a wall with a stairwell or slamming doors, and occasionally from sources outside the laboratory such as nearby construction, traffic or trains. Environmental vibration can be reduced with anti-vibration pads placed under the feet of the apparatus.

Centering

Proper centering is essential for reproducible hydrodynamics in the dissolution test environment. USP <711> specifies centering be < 2 mm. A tighter specification of <1 mm, which offers a more appropriate centering specification given the tightness of the current specifications, is described in the mechanical qualification procedures by the FDA and ASTM, as well as the USP Toolkit 2.0. Centering rings can vary from vendor to vendor, and it is recommended to use the centering rings from the manufacturer of the dissolution apparatus to ensure optimal centering. Also, centering rings or collar devices should be tight and if they have fingers to center the vessel from the internal surface, all should be in place. Loss of one or more fingers in the centering ring or using a faulty collar can greatly reduce the proper centering of the vessel.

Vessel Verticality

Vessel verticality is not a required test per USP <711>, but is a recommendation of the USP Toolkit 2.0 and mechanical qualification procedures. Vessel verticality, like centering, is essential for reproducible hydrodynamics from vessel to vessel. To ensure vessel verticality, it is important that both an appropriate vessel is used and the attachment of that vessel to the vessel plate is tight.

Vessel quality can vary by vendor (6) and it is important to use a reliable vendor for vessels, preferably sourced from the manufacturer of the equipment. Either glass or plastic vessels are acceptable for use with the PVT and other dissolution testing, although there is little difference in results between them based on testing performed at Agilent. Because plastic vessels are molded and identical to one another, some feel that this gives better assurance to the dimensions and quality of the vessel, as opposed to a traditional hand-

blown glass vessel that may vary from vessel to vessel, especially in poor quality vessels.

Vessels should be kept in the same position and orientation from test to test to enable proper traceability, data trending and failure investigation. It may also be advisable to keep the orientation of each vessel constant in order to ensure centering is the same from test to test. Orientation can be kept constant by making a mark on the top of the vessel and on the vessel plate so that they can be lined up in a consistent manner from one run to the next.

Vessel should also be securely attached to the vessel plate. This is especially important since a 500 mL test may produce semi-buoyant vessels which can not only impact the verticality of the vessel, but can induce vibration as well. In the case of an EaseAlign ring system, the 0-rings should be tight and fit securely onto the pegs without wobbling. Clip attachment systems should fit tightly on the vessel and collar systems should fit snugly. Use of an Agilent TruCenter vessel with magnetic attachment keeps the verticality under tight control and prevents any vessel movement due to buoyancy. PVTs run with the TruCenter vessel attachments showed some improvement in the %CV versus the EaseAlign ring attachment system and may improve PVT outcomes.

Dissolution Components

Dissolution components play an equally important a role as they ensure a reproducible and stable dissolution environment. These components include vessels, paddles, baskets and basket shafts.

Vessels

In USP <711> the criteria for vessel tolerances are quite wide, and depending on the vendor used, there may be different targets within the range or acceptable variations within the USP range. Additionally, there are options available for both plastic vessels and molded glass vessels which are considered ideal since they are identical from one to the next and offer consistency.

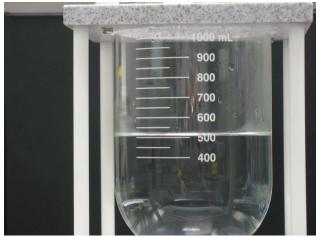
To demonstrate the variance often found in vessels, Agilent performed a sample test using the Agilent 7010 dissolution apparatus with various vessel types and sources including:

- Varian/VanKel EaseAlign glass vessel
- Generic glass vessel
- · Agilent plastic vessel
- Agilent TruCenter glass vessel
- Agilent TruAlign glass vessel*

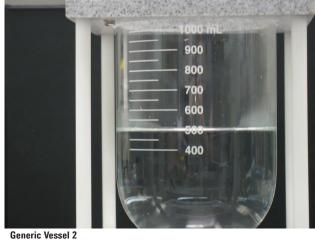
Vessel Type	% Pass	%CV	Mean
EaseAlign	92%	5.2%	32
TruCenter	100%	4.3%	33
Mixed Set	57%	4.8%	34
Generic	33%	6.3%	33
TruAlign*	100%	4.4%	33

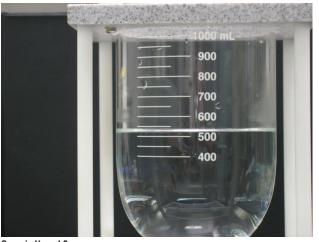
 $\label{thm:constraint} \textbf{Table 1.0 Agilent PVT Data Collection Study}. Use of Agilent vessels demonstrated a much higher \% pass rate and lower \%CV in comparison to generic vessels and mixed sets of vessels. Overall mean is relatively unchanged between various vessel types.$

^{*}Testing completed on Agilent TruAlign glass vessels was performed on the Agilent 708-DS Dissolution Apparatus.

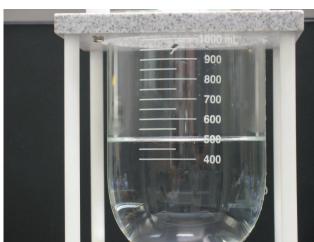


Generic Vessel 1





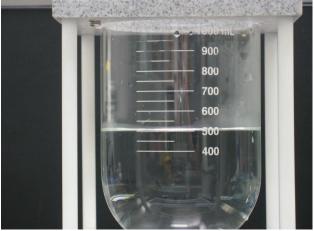
Generic Vessel 3



Generic Vessel 4



Generic Vessel 5



Generic Vessel 6

Variation in Vessel Dimensions. In a set of generic vessels from the same manufacturer, varying volumes according to the measurement scale on the vessel are shown by adding exactly 498 g of water to each.

Regardless of the type of vessel used, the means were fairly similar to one another between data sets and tended to be in the low side of the range for the PVT. The %CV was markedly different, however, and seemed to fall into 3 populations. The best results came from the TruCenter vessels and TruAlign vessels. The next best results were for EaseAlign glass and plastic vessels, and the worst (and only failing results) were from generic vessels.

These results seem to indicate a few conclusions. One conclusion from this study is that there does not appear to be a difference in %CV between a molded vessel and a blown vessel from Agilent, and that slight vessel differences may not play a role in higher %CV.

The second conclusion is that proper vessel attachment plays a role in the %CV. Attachment with the TruCenter kit may better maintain the vessel vertically than an EaseAlign system, and also keeps them more stationary, thus reducing vibration and swaying of the vessel caused by buoyancy.

The final conclusion is that generic vessels are variable enough that they do impact the %CV of the dissolution test and can result in a higher tendency for failing results. Data gathered from Agilent's chemists seems to support this, as a higher failure rate exists for generic vessels. Interestingly, the highest failure rate seen is associated with systems having a mixture of generic and vendor vessels indicating that there may be different targets for the various vessel measurements between vendor vessels and generic ones.

Paddles

Paddles should comply with the specifications listed in USP <711> for wobble, verticality, and physical dimensions. In addition, paddles should be in good condition. If the finish on stainless steel paddles appears flat and gray, there is corrosion on the paddle and it could result in a greater chance of adsorption of drug. If a PTFE-coated paddle is used, it needs to be free to scratches, fine protrusions of PTFE, etc. These are additional sources of surface area and result in greater and more variable hydrodynamics in the dissolution vessel, causing higher means and %CV. Degradation of the PTFE paddles can be areas for air bubble attachment, as well as other issues.

Paddle height should be properly set and tightly maintained, with paddle heights at 25+/- 1 mm to allow more reliable results with the PVT. The paddle height setting is a parameter to which the PVT seems particularly sensitive.

Baskets

Basket condition is an important criterion for proper and reproducible dissolution testing. Baskets should be shiny and free of corrosion.

Baskets should be checked against deformities, intention on the bottom and no excessive wobble. Indentation on the bottom of the basket often arises if a spherical ball is used to set the height. Residues should be checked for and thoroughly removed if found, as they tend to occur on the seam between the bottom and sides of the basket.

Baskets may be cleaned by rinsing gently with warm DI Water, followed by ultra sonication in a beaker with methanol or ethanol, then air dried. This should remove residues from the basket and also allow them to become very dry as required for the PVT test since prednisone is very sensitive to environmental moisture. Note that the PVT only applies to the traditional 40-mesh design basket and does not apply to 36-mesh baskets, which are also presently contained within the International Conference on Harmonisation (ICH) specifications contained in the USP.

Basket Shafts

The same criteria for paddles above should be followed for basket shafts.

Analytical Technique

Analyst technique and the procedure used can greatly impact the dissolution test. Dissolution is a technique-dependant test in some aspects, and a variety of steps in the dissolution process can induce error. This begins with the degassing of the media and concludes with the

This begins with the degassing of the media and concludes with the filtration of the samples that end the dissolution process.

Media Preparation

Media should ideally be prepared and degassed per USP specifications. Per USP, the media should be heated to 450 C (although references for 410 C and 41-450 C are found in different USP documents), then vacuum degassed through a 0.45 μm PVDF filter, and then held under vacuum for an additional five minutes. This procedure essentially is boiling the media at a lower temperature under a vacuum which effectively removes dissolved gases in the media.

If using an alternate degassing step, it should be verified to achieve similar levels of degassing using a dissolved gas meter to demonstrate that <6 ppm oxygen (7) is achieved. One of the most common degassing procedures used is helium sparging. This can be an effective way to remove gases from the media by replacing them with a more inert gas, helium. This method is generally acceptable for use with the PVT as long as the helium is sparged with a consistent flow rate, a specified diffusion system, such as airstone, for adequate period of time. A sparging level involving at least 15 minutes with a flow rate of 4-6L/ minute with an airstone equipped on the inlet to ensure reproducible and full deareation of the media was found effective in the Agilent studies, and requires validation against the USP method.

Other alternatives including sonication and nitrogen sparging are not effective for use with dissolution. Sonication and sonication under vacuum do not work well for aqueous-only media. Nitrogen sparging is replacing air with its largest component which can actually increase dissolved gas relative to untreated media, and bubbles are usually present after these methods are employed.

Media Pouring

Media pouring can induce two sources of error or variability to the dissolution test. The first source is the volume accuracy of the media being poured, and the second source is reaeration of the media during the pouring process.

Accuracy of media volumes depend on the method of media measurement. The most common means of measuring and delivering media is using a Class A 500 mL or 1L graduated cylinder, which offers a volume of +/- 1% accuracy from the measured volume. This translates to at least a 1% source of variability when using a 500 mL flask and 2% for a 1L cylinder, not accounting for human error.

Ideally, media should be weighed to 498 g according to the USP certificate for lot P1I300. This allows a much tighter control of volumes and it is quite easy to achieve weights +/-1 mL of the target, which is approximately +/-0.2 % and essentially eliminates this as a source of error. It also allows for documentation of the volume to eliminate volume from any potential investigations.

Media reaeration is a potential source of error that needs to be controlled. To prevent the media from reaeration, the media should be measured and poured as soon as it is degassed. Then the dissolution test should begin once the media reaches approximately 37° C. It is also important that the media does not cool down below 37° C before coming up to equilibration, as this will lead to greater levels of reaeration.

Other than transferring the media in a timely manner, it is also important to pour the media gently to avoid mixing with as little air as possible. Media should be poured along the shaft or back wall of the dissolution vessel slowly to achieve this. In regards to reaeration, weighing media offers the additional advantage of only needing a

single pour from the vacuum flask to the dissolution vessel. A graduated cylinder, on the other hand, requires pouring into the cylinder and then into the vessel. Weighing into a dissolution vessel directly can be accomplished by placing the vessel onto a top loading balance with a cork ring, or ring stand device and tare the balance. Then pour 498 g of media into the vessel per the prednisone certificate and bring it back to the dissolution apparatus. (4)

During media temperature equilibration in the vessel, it is important to not allow the paddle or basket to rotate in the media as this will create a different set of hydrodynamics from test to test. It also encourages tablets landing offcenter in the vessel as the tablets may be caught in the currents created during equilibration. Ideally, the paddle or basket shaft is lowered into the media during equilibration to prevent a temperature drop at the time of the test if a room temperature shaft was placed into the 37o C vessel. In the base of the basket shaft, it is important to wipe the bottom of the shaft off prior to adding the baskets and beginning the test.

Tablet Introduction

Tablets should be introduced in the same fashion consistently by the analyst. Introducing the PVT tablet vertically from a position near the paddle will offer the best chance for having a centered tablet. Off-center tablets can land in areas of greater vessel perturbation and result in higher or inconsistent results.

It is acceptable to stagger paddle starts to allow for ample manual sampling time later in the run. A calibrated timer should be used and times of drops recorded in order to sample at the correct offsets at the sampling time. Staggering drops is only possible on dissolution apparatus where spindles can be individually controlled so that they are not rotating

prior to dropping the tablet in a given position.

Once tablets are dropped, replace the evaporation covers if they have been removed, and let the test continue.

Sampling

Sampling should be performed manually, and automated sampling for the PVT is discouraged by the USP unless the method has been properly validated. Sampling should be taken in the zone specified by the USP which is halfway between the top of the paddle blade or basket and the top of the media, and no closer to the vessel wall than 1 cm. This is a fairly small area, and it requires skill to perform it accurately in six to eight vessels within the time limits of +/-36 seconds from 30 minutes, assuming no stagger is performed. Ideal sampling is performed in a sitting position at eye level with the dissolution vessels for a visual check of sampling location prior to the sample pull.

Filtration

Filtration should be performed within the same 2% window of the timepoint as sampling per USP. Until filtration occurs, the sample will continue to dissolve and add variability and higher dissolution rates. During the sampling process, there is violent movement of the dissolution sample through the cannula and syringe which creates a more aggressive dissolution environment than inside the dissolution vessel. Use of a cannula filter, such as the Full Flow Filter, can immediately filter the sample. Alternatively, if a syringe filter is used, the filtration should occur immediately after the sample is taken and before the next sample is taken, which is where a staggered start is particularly needed.

Conclusion

In conclusion, the USP PVT offers a genuine benefit to dissolution laboratories. Ironically, the FDA Draft Guidance for utilizing mechanical qualification procedures indicates that "appropriate measures be taken to control the following sources of significant variability in dissolution testing: dissolved gasses, vibration and vessel dimensions." (8) The traditional USP PVT with prednisone is particularly sensitive to these areas and Agilent believes the PVT is a valuable tool in maintaining proper dissolution apparatus qualification. As with any procedure, analysts must be properly trained in preparing for and conducting dissolution tests. Ultimately, Agilent's goal is to provide a dissolution apparatus that has been properly qualified, maintained and suitable for the purpose of ensuring conformance to product performance.

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