Frequently Asked Questions

Performance Verification Tablets (Prednisone Tablets)

Where are the acceptance criteria for the new lot of Prednisone Tablets? I have heard that you have to calculate the geometric mean and %CV of your data. How is that done?

The certificate for Prednisone Tablets RS Lot P1I300 gives the acceptance criteria and formulas for the calculations. Access this (8)certificate (prednisone LotP1I300) online ⬇ (128KB). Although the certificate provides the procedure for calculating the geometric mean and %CV for your Performance Verification Test (PVT) data, a more detailed discussion was provided in a Stimuli to the Revision Process article by Walter Hauck, et al., entitled "(9)Description of the Upcoming Change in Data Analysis for USP Dissolution Performance Verification Tests" ⬇ (527KB), PF 34(6) [Nov–Dec 2008]. To help analysts with this calculation, USP has provided a Web-based tool; see (10)Calculation Tool for the PVT of Dissolution Assemblies.

How many runs have to be performed for the Performance Verification Test?

USP's current approach for the PVT calls for the performance of two consecutive runs including all positions of a dissolution instrument (Single-Stage Test approach). The combined results for both runs will be evaluated and compared with the acceptance criteria corresponding to the Single-Stage approach.

Moreover, USP has implemented a Two-Stage Test approach that allows the analyst to evaluate the results of the first run and compare it with the acceptance criteria corresponding to the first stage (run) of the Two-Stage approach. If the results are within the first-stage acceptance criteria, the PVT test can be stopped at this stage.

In case of an assembly with 12 positions, a single run (with all positions tested) is required for the PVT.

Did the method to perform the PVT of Lot P1I300 change from the previous lot?

The method to perform the PVT has not changed from the previous lot. USP provides some recommendations to help customers achieve a successful PVT. These details are given in the (11)Certificate of the USP Prednisone Tablets RS Lot P1I300 ⬇ (128KB) as well as in the (12)Dissolution Procedure Toolkit, version 2.0 ⬇ (280KB).

What is the source of Lot P1I300?

USP Prednisone Tablets Lot P1I300 is a continuation lot for Lot P0E203.

Will USP publish a paper detailing the results of the collaborative study?

Yes. USP is preparing a paper that will cover the results of the collaborative study and how the final limits for Lot P1I300 were established.

If it is obvious after the first run that the instrument will not pass the PVT, do I still need to perform the second run?

No. The lab can stop after the first stage (run). However, after any adjustments to equipment, test procedure, and so on, the PVT must be restarted with a new first run. Please also see the answer to question 8.

Why is there not both a re-test limit and a failure limit for the %CV for the first stage of the Two-Stage approach?

There are circumstances when there is no point in performing the second stage. As an example, consider the following Apparatus 2 data:

Stage 1: 30.615, 29.875, 34.473, 27.824, 38.327, 33.159, 30.795 (actual data) GM=32 passes, %CV=10.6 fails

Stage 2: 32.000, 32.000, 32.000, 32.000, 32.000, 32.000, 32.000 (possible data) combined GM=32 passes, combined %CV=7.5 fails

USP agrees that a failure (futility) limit would be useful. See the table below. If the %CV after the first stage equals or exceeds the value in the table (without rounding), then it is impossible to meet the %CV criterion after the second stage. If a laboratory wishes to use these "futility" factors in running the Two-Stage option, USP recommends this be part of the laboratory's standard operating procedures for this approach. Please also see the answer to question 6.

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Futility Factor

(%CV at or above value given, second stage testing will not produce passing result)

No. of Vessels

Apparatus	6	7	8
1	14.9%	14.0%	13.9%
2	9.6%	9.5%	9.2%

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Why do the acceptance criteria use the geometric mean rather than arithmetic?

Experience with this lot of Prednisone Tablets RS and prior PVT collaborative studies has shown that the data are better analyzed in the log scale to improve the normality assumption. The acceptance limits are actually for the arithmetic mean and standard deviation in the log scale. The limits are converted back to the percent dissolved scale to make them more interpretable. This conversion changes the arithmetic mean and standard deviation into a geometric mean and %CV. See the (9) Description of the Upcoming Change in Data Analysis for USP Dissolution Performance Verification Tests (527KB) for details.

The %CV requirement in the new acceptance criteria seems incredibly tight. We have data that pass the current Lot P0E203 ranges and yet would fail the new criteria based on the %CV requirement. Has USP made the test more difficult to pass?

There was no intent to make the test more difficult to pass. However, it is different, so some data that would pass the previous test could fail the new one and vice versa. The %CV requirement is based on the estimate of within-laboratory variability from the participants in the collaborative study for Lot P1I300.

Have the storage conditions been changed for USP Prednisone Tablets RS Lot P1I300?

Historically, this standard has been stored at room temperature. Lot P1I300 should be stored in a dry place at 15°–25°.

Can I round the dissolution results to whole numbers for calculation?

Per General Notices, intermediate results are not to be rounded. In particular, the percent dissolved values should be retained to at least three decimals prior to calculation of the geometric mean and %CV.

What should I do if the PVT for Apparatus 1 passes and then fails for Apparatus 2?

If nothing but the stirring elements are changed when switching from Apparatus 1 to Apparatus 2, then the PVT for Apparatus 1 is considered to be successful. In this case, the PVT has to be repeated for Apparatus 2 only.

Is the Calculation Tool for the Performance Verification Test (PVT) of Dissolution Assemblies validated?

USP validated the Calculation Tool based on USP's internal procedures and guidelines. A document describing the processes will be posted on the USP Web site.

I failed %CV with the new lot. What should I do?

The limits on %CV are to ensure that the dissolution test assembly acts as an integrated unit. When a dissolution assembly fails to pass the %CV limit, we recommend that lab personnel check the equipment and test procedure according to USP's published(12)Dissolution Procedure Toolkit, version 2.0 (280KB), make the necessary adjustments, then repeat the PVT.

What is the difference between Lot P0E203 and Lot P1I300?

Please see (13)Notice to Purchasers of USP Prednisone Tablets Lot P1I300 Concerning Relabeling (188KB).

Why is there a difference in the %CV acceptance limits between the Single-Stage and the second stage of the Two-Stage tests? Shouldn't they be the same?

The current approach for the PVT is designed as a Single-Stage approach consisting of performing two consecutive runs. This means that for an 8-position dissolution assembly, 16 individual values are generated and evaluated together at the end of the second run.

A laboratory may choose to implement the PVT as a Two-Stage approach (group sequential design). The Two-Stage approach allows the possibility to stop the test at the first stage (run); however, a kind of penalty has to be paid for the possibility of stopping after the first stage (run). This is to control the probability of falsely passing the test—the more opportunities there are to pass, the higher the false pass rate will tend to be. In the acceptance table for the Two-Stage approach, the accept/reject decision rules are more stringent at the first stage than at the second. The penalty is that the acceptance values for the second stage (run) are tighter than those of the Single-Stage approach although the number of the individual values evaluated is the same. (If the limit at the end of the Two-Stage design were the same as for the Single-Stage, there would necessarily be an increase in the false pass rate owing to the possibility of passing at the first stage.) The first stage values were chosen to make the second stage values similar to those from a Single-Stage test. It happens that the limits for the geometric mean appear not to change, but that is due to rounding and would show the same penalty if shown to more decimals.