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RESEARCH PAPER

Establishing New Acceptance Limits for Dissolution Performance Verification of USPC Apparatus 1 and 2 Using USPC Prednisone Tablets Reference Standard

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ABSTRACT

Purpose On 1 March 2010, the US Pharmacopeial Convention released into commerce Lot P11300 of its Prednisone Tablets Reference Standard for use in periodic performance verification testing (PVT) of dissolution Apparatus 1 and 2. This report presents the collaborative study data, development of the acceptance limits, and results from supporting work for this Lot.

Methods The collaborative study involved 25 collaborators who provided data for Apparatus 1 and 31 who provided data for Apparatus 2. These limits are for the geometric mean and percent coefficient of variation (%CV) instead of per-individual results as for prior lots. Stability of results and sensitivity to test performance parameters were also studied.

Results To determine new PVT acceptance limits, the authors calculated geometric mean and variance components as percent coefficient of variation. The move to the geometric mean and %CV criteria brings the acceptance criteria in line with current accepted statistics and provides a more realistic assessment of the system's performance. Results for Apparatus 1 are stable over time, but for Apparatus 2, the mean decreases over time. Acceptance criteria are adjusted for this trend. Lot P1 demonstrates sensitivity to test performance parameters (vessels and degassing).

Conclusions Apparatus 1 results are stable over time. Those in Apparatus 2 show a decrease over time in the geometric mean but show no trend in variability. The current tablets are shown to remain sensitive to two operational parameters, degassing and vessel dimensions, not covered by mechanical calibration. The new acceptance limits for Lot P1 are based on geometric mean and %CV for Prednisone Tablets Reference Standard Lot P11300. The limits better control variability than the prior per-individual-result limits.

KEY WORDS dissolution · performance verification · prednisone reference standard tablets

The opinions expressed here are those of the authors and do not represent the official position of the US Food and Drug Administration or the US government.

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INTRODUCTION

The dissolution procedure described in *US Pharmacopeia* (*USP*) General Chapter "Dissolution" <711> is used to measure the *in vitro* performance of nonsolution solid oral dosage forms (1). The procedure can function both as a quality control tool and, under specified circumstances, as a predictor of the dosage form's performance *in vivo*. Thus, the procedure is widely used as a performance test in a drug product's private or public specification. Dissolution results may exhibit at times a high degree of variability. This variability may be due to the dosage form itself but can also arise from the dissolution measurement. Via its reference standard (RS) program, the United States Pharmacopeial Convention (USPC) maintains standardized materials that are used in a periodic performance verification test (PVT) to ensure the integrity of dissolution results (2,3). For USPC dissolution Apparatus 1 (basket) and Apparatus 2 (paddle) the PVT RS is a 10-mg prednisone disintegrating tablet formulation. The PVT assesses the assembly, analyst performance, and analytical procedure (4). The PVT

procedure does not result in a direct drug product measurement but is based on a well-characterized model dosage form that is of value in verifying the performance of the test apparatus (performance verification, or PQ, in the language of GMP).

USPC Prednisone Tablets RS Lot P1I300 (Lot P1) has been released as the replacement for Lot P0E203 (Lot P0). Lot P1 is a continuation lot—that is, P1 and P0 are from the same manufactured batch (Lot P) of the reference material. References to "Lot P" apply to material from this manufactured batch labeled either as P0 or P1. Starting with Lot P1, available in commerce as of 1 March 2010, the acceptance criteria for the dissolution PVT changed from one for individual results (*i.e.*, individual dissolution vessel positions) to one indicating mean and variance for all positions of a dissolution assembly (*i.e.*, the result calculated is for a geometric mean indicative of trueness and percent relative standard deviation (%RSD) indicative of precision) (5). This new approach for setting the PVT acceptance criteria brings the USPC standard into alignment with ISO International Standard 5725 (6). This paper presents the results from the collaborative study and allied supporting work, with emphasis on the determination of the new acceptance limits for Lot P1.

METHODS

Stability Studies

For the evaluation of stability, samples of the Lot P reference material were stored under controlled storage conditions at 25°C and 50% relative humidity (RH). Samples were pulled, and their dissolution behavior was investigated, at two-month intervals for the first 6 months after their storage and every 3 months thereafter. These investigations included tests on two different dissolution instruments using both USPC Apparatus 1 and Apparatus 2. Two analysts performed the tests, each performing two tests on each apparatus and instrument.

Parallel to this study, investigations on Lot P samples stored in USPC's warehouse were conducted with the protocol described above. USPC's warehouse environment is controlled regarding temperature (20°C) but not humidity. (Studies not reported here have shown that the tablets are sensitive to temperature but not humidity.) Dissolution experiments in this case were performed only using USPC Apparatus 2 on two dissolution instruments. Two runs were conducted on each dissolution instrument at each time by a single analyst. In both studies the same dissolution instruments were used over the entire time period in order to reduce potential instrument-induced variability.

The stability trend for each study was evaluated by fitting a regression model to the data. First, linear models were fit in the original and log% dissolved scales. That in the log scale fit the data the best. Then, a quadratic was attempted, but the fit was improved only trivially and so was not used. Thus, the final model was linear in the log scale.

Study to Confirm the Sensitivity of the Reference Material

A previous study conducted on Lot P0 showed that insufficient degassing of dissolution medium and the quality (consistency of dimensions and irregularities on the inner surface) of the glass vessels are critical parameters that affect PVT results (7). Another study conducted to investigate the effect of using vessels obtained from different sources on the dissolution results of the Prednisone Tablets RS demonstrated that using vessels from different sources not only influenced the amount of prednisone dissolved but also contributed to differences in amount of variability observed in dissolved prednisone values (8,9). Although the dissolution vessels characterized in these experiments meet the current specifications found in *USP* <711>, there were significant differences in both the geometric dimensions and irregularities for sets of vessels obtained from different commercial sources.

The current study was conducted to confirm the outcome of the previous studies and to show that the Prednisone Tablets RS remained sensitive to Apparatus 2 operational parameters (degassing and vessels). For this purpose, we used vessels that generated results with high variability in prior work (8). The vessels had dimensions that were variable, though still within the limits specified in the compendia. One USPC Apparatus 2 dissolution instrument was used for the study, and one test for each deliberate modification (degassing and vessels) was performed.

Collaborative Study

A collaborative study was conducted in mid-2009 to establish the acceptance criteria for Lot P1 for the Apparatus 1 and 2 dissolution PVTs. Forty-one collaborating laboratories were selected based on a USPC headquarters staff review of each laboratory's existing quality system. Among the participants are USPC, regulatory agencies (US FDA, Health Canada, Health Sciences Authority Singapore, and Thailand Bureau of Drug and Narcotic) and industry laboratories in the US and elsewhere. The collaborators tested in a blinded fashion two lots of USPC Prednisone Tablets, Lot P (named P0 at the time of the collaborative study) and an additional, newly manufactured, Lot Q, to

determine the acceptance ranges for the Apparatus 1 and 2 dissolution PVTs at 50 rpm and 30 min. Two analysts (analysts 1 and 2) at each laboratory tested five blinded samples per each apparatus. Analyst 1 tested three samples (two blinded Lot Q and one blinded lot P), and analyst 2 tested two samples (one blinded Lot Q and one blinded Lot P). Each experiment consisted of six, seven, or eight tablets, depending on the configuration of the laboratory's instrument. This report considers results only for Lot P.

Within 6 months of the start of the collaborative study, all laboratories conducted mechanical calibration (10) and PVT tests using unblinded Prednisone Tablets Lot P0 and Salicylic Acid Tablets Lot O0D200. All unblinded data reported met the acceptance limits applicable at that time based on the individual values for both Lot P0 and Lot O0D200, and all instrument parameters were within the mechanical calibration ranges specified in chapter <711>.

Statistical Analyses

For analysis of the collaborative study data, the statistical method employed was a restricted maximum likelihood (REML) estimation of a nested, random-effects model separately for the two apparatus. Specifically, experiments were nested within collaborators, and collaborators and experiments were random effects, leading to estimates of between-collaborator and between-experiment variance components. Analyses were done in SAS for Windows, Version 9.1 using Proc Mixed. The default variance components covariance structure was used. This analysis estimated three variance components for Lot P: inter-collaborator, inter-experiment, and residual (between-position, within-experiment). According to study protocol, each of two analysts conducted one experiment with separate samples for Lot P. The "experiment" component thus included contributions from sample and analyst. The between-position variability included assay variability, any variability associated with tablet position in the vessel, variability in the vessels used, and tablet-to-tablet variability.

The acceptance limits were determined as reported earlier (5,11) with exceptions as noted below. The single-stage test acceptance limits for the geometric mean were determined from the collaborative study mean in the log scale, plus and minus two standard deviations, where the standard deviation is the reproducibility standard deviation for the mean. For two sets of six tablets (12 tablets total), for example, this would be $exp\left(\overline{X} \pm 2\sqrt{S_C^2 + S_E^2/2 + S_R^2/12}\right)$ where $\overline{X}$is the sample mean in the log scale, the three S^2 are the three variance component estimates, and the *C*, *A*, and *R* subscripts denote Collaborator, Analyst, and Residual (between-position). The *exp* converts the acceptance limits from the natural log scale back to the percent dissolved scale. For the between-position variance in the log scale, the upper limit was found as $18.31*S_R^2/10 = 1.831*S_R^2$ for two sets of six tablets, where 18.31 is the upper 5^{th} percentile of a chi-square distribution with 10° of freedom. For 7-, 8-, 12-, and 14-position assemblies, the degrees of freedom were 12, 14, 11, and 13, respectively.

The limits for the two stages of the two-stage option were determined as published (5,11) with one exception. As published, the limits for the first stage of the two-stage test

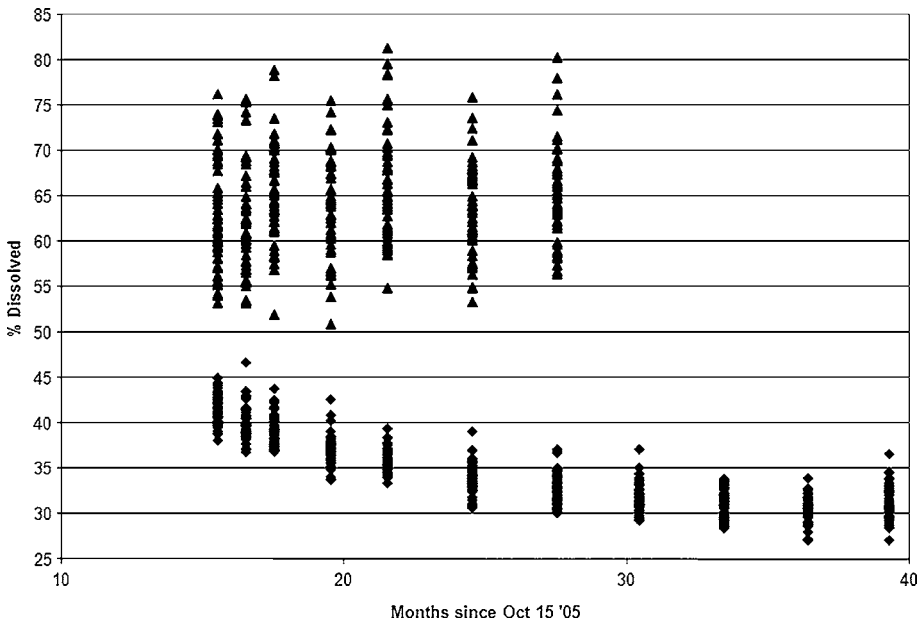

Fig. 1 Stability Trend at 25°C/50% RH of the Prednisone Tablets RS, Lot P, in USPC Apparatus 1 and Apparatus 2. Apparatus 1 data are shown as triangles; Apparatus 2 data are shown as diamonds.

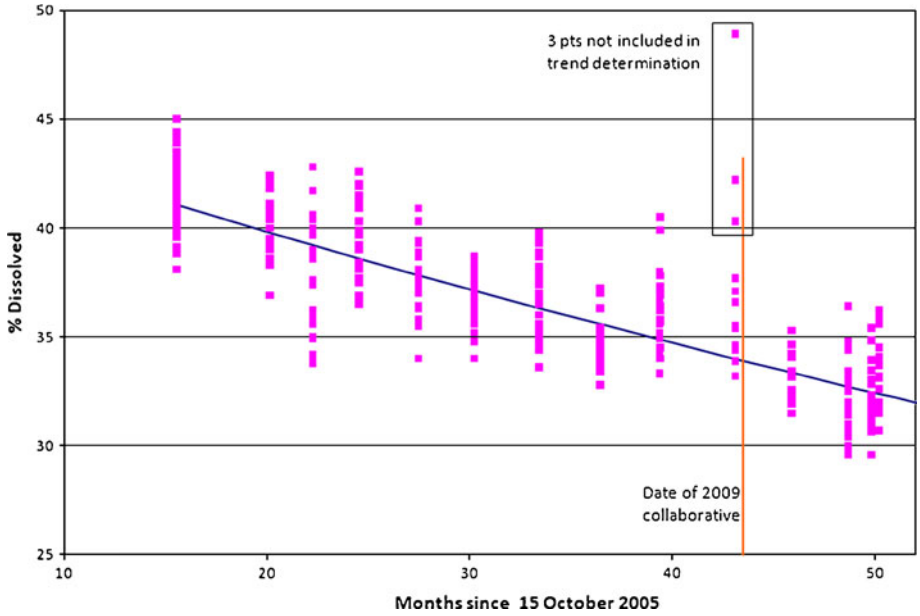

Fig. 2 Stability Trend for Apparatus 2, Warehouse-Stored Tablets (20°C). The solid curve is the mean trend for the stability data (*squares*). The trend is linear in log % dissolved.

were determined as for the single-stage test but used 60% confidence rather than 95% confidence, making the intervals narrower. For the second stage of the two-stage test, the limits were determined to preserve the operating characteristics (probabilities of passing) from the single-stage test. The exception was that, for the geometric mean limits at the first stage, it was found that the interval could be widened from 60% confidence to 75% confidence without materially changing the operating characteristics of the test. In addition, the limits at the second stage could be kept the same as for the single-stage test. This change made the first-stage limits for the geometric mean slightly wider than would otherwise have been the case.

All estimated variances and variance components, S^2, and the upper acceptance limits for the between-position variance in the natural log scale were transformed back to percent coefficient of variation (%CV) in the original, percent dissolved scale using the lognormal formula, $\%CV = 100\%*\sqrt{\exp(S^2) - 1}$.

RESULTS

Stability Studies

Results of the stability study conducted at controlled storage conditions (25°C and 50% RH) for Lot P Prednisone tablets tested with Apparatus 1 and Apparatus 2 are summarized in Fig. 1. The percent of the reference material dissolved at 30 min in Apparatus 1 appeared to be stable with time. For Apparatus 2, a decrease in the percent dissolved is observed. In addition, the variability for both apparatuses appeared unchanged across time.

Table I Confirmation of the sensitivity of the reference material

Position	Baseline Run 1	Baseline Run 2	Non-Degassed Medium	Vessel with Less Consistent Dimensions
1	36.4	37.3	63.1	35.1
2	37.3	34.0	67.7	36.2
3	37.2	35.5	65.5	41.6
4	36.3	36.4	65.5	35.7
5	36.4	35.7	72.7	37.6
6	39.3	37.3	65.0	35.1
GM	37	36	67	37
SD	1.2	1.2	3.3	2.5
%CV	3.0	3.5	4.9	6.5
PVT	passes	passes	Fails GM	Fails %CV

Results of the stability study for warehouse-stored Lot P Prednisone tablets tested with Apparatus 2 were used for the evaluation of the rate of decrease in the dissolution results. The results are summarized in Fig. 2. The stability data analysis shows that a decrease in the mean dissolution value follows a log-linear trend (linear in the log% dissolved scale) as shown by the fitted trend line shown in Fig. 2. The trend is for a percentage drop of approximately 2%–3% per year for the mean percent dissolved when using Apparatus 2. As with Fig. 1,

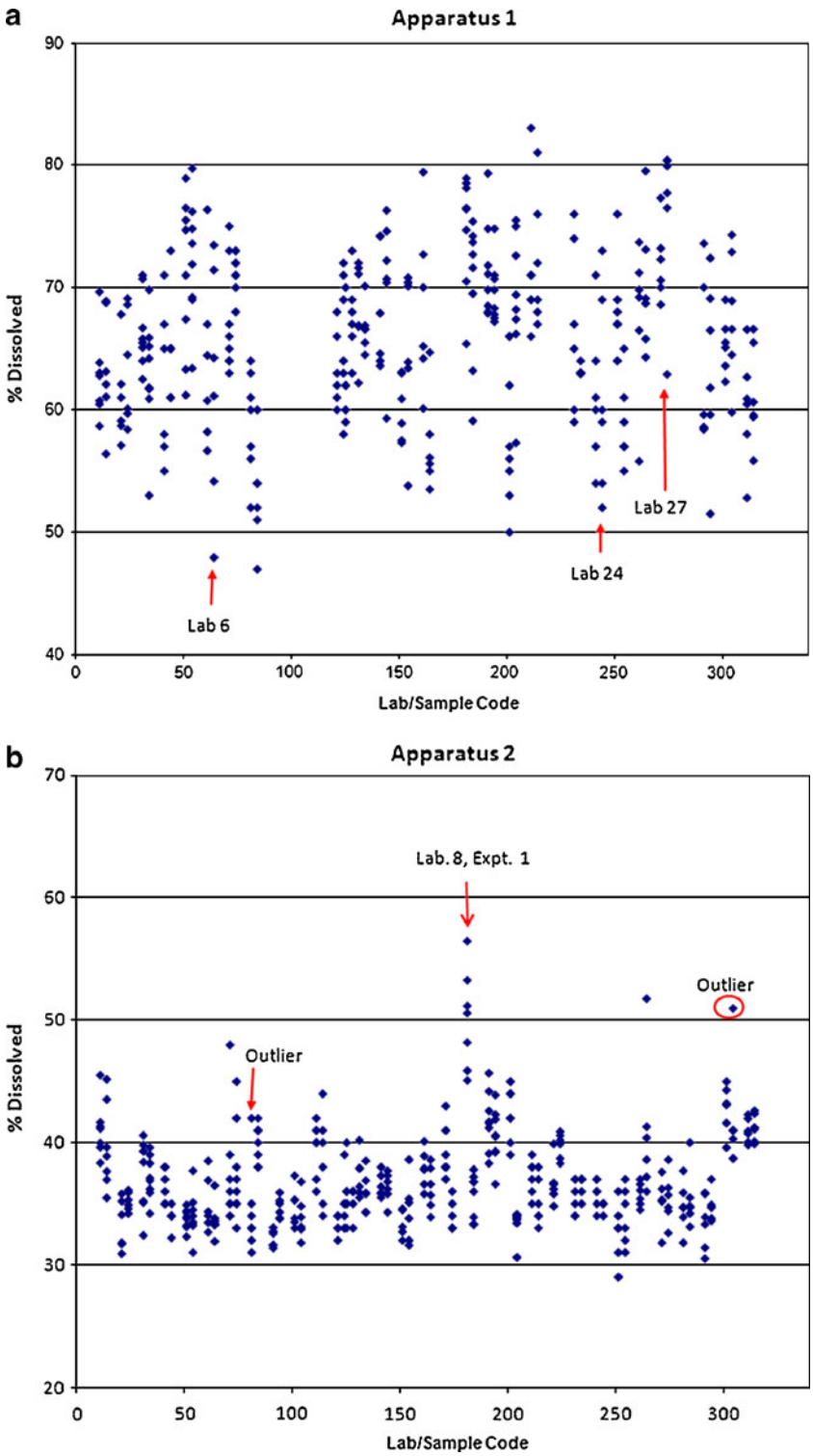

Fig. 3 All Data (before Any Exclusions). Notes: The X-axis is a code that identifies the combination of laboratory and experiment. All tablets for an experiment are in a vertical line. The two experiments for a laboratory are close horizontally relative to the distance to the data for the next laboratory. Laboratories and values marked are those listed in Table I.

there is no indication of a change in the variability of results over time. Months 56 and 59 data, obtained recently and not used in determining the trend, were compared to the projected trend. The geometric mean of 12 values was 31.7 at month 56 compared to the predicted trend value of 31.1 and 31.5 at 59 months compared to the predicted trend of 30.5. These new results are consistent either with the trend or some flattening of that trend. As described below, the acceptance limits are set to allow for either possibility.

Study to Confirm the Sensitivity of the Reference Material

The effects on the PVT results of the deliberate changes in the extent of degassing of the dissolution medium and the use of vessels with more variable dimensions are shown in Table I. When the medium was not degassed, there was a significant increase in the values of % prednisone dissolved. The use of vessels that were shown to have variable dimensions resulted in the increase of the variability of the individual results. These results are consistent with these tablets remaining sensitive to critical dissolution parameters throughout the stability time period. For both changes, the results here show the same pattern as in previous studies (7). As noted above, all vessel dimensions were within the limits specified in general chapter <711>.

Collaborative Study

Twenty-five collaborators provided data for Apparatus 1, and 31 provided data for Apparatus 2. Fig. 3 shows all the data obtained from the collaborative laboratories before any exclusion. In this figure, each symbol is one tablet, and a vertical set of six to eight symbols is one experiment. There is more within-experiment variability for Apparatus 1 than for Apparatus 2.

The data were screened in three steps, as follows:

1. The information received was screened for protocol violations and for PVT acceptability using blinded Lot P data for both the current criterion based on individual values and the new GM/%CV criteria. For the latter, the limits used were those published for the single-stage test (11). Table II lists the combinations of laboratory and apparatus that did not meet one of these conditions. The three laboratories failing the PVT criteria are marked on Fig. 3. In addition to the data shown in Table II, nine laboratories failed the geometric mean PVT requirement to the low side for Apparatus 2 (lowest geometric mean (GM) of 33.3 compared to a limit of 34.5), one of which was also low for the individual value for PVT (29 *vs.* limit of 30). These laboratories are not dropped for the Apparatus 2 analyses because of the drop in Apparatus 2 values for Lot P since the current limits were determined. Two laboratories also failed the PVT to the high side for Apparatus 1 (83 *vs.* 82 per tablet and 72.2 *vs.* 71.6 GM). USPC stability data showed that Apparatus 1 values may have been trending slightly higher on average than at the time of release of Lot P0, and so these two laboratories were kept in the Apparatus 1 analyses.
2. The exclusions of Step 1 were applied, and then the data were analyzed using the nested model described above (to obtain variance estimates) and then using Xbar and S control charts (in the natural log scale). These control charts identify individual experiments whose mean or variability is unusual relative to the other values in this study. For the Xbar charts, 3-sigma limits were applied using the reproducibility standard deviation (square root of the sum of all estimated variance components). Three-sigma limits correspond to 0.0027 probability in the two tails combined. For the S control charts, the same two-

Table II Laboratories and Data Excluded from Collaborative Study Analyses

Screening step	Laboratory	Apparatus	Experiment	Reason
Protocol violations	12	Both	Both	Provided two sets of data from different instruments; kept the data from the instrument with the better mechanical calibration data
	7	Both	Both	Non-USP degassing method
	26	Both	Both	No vessel ID data
PVT failures	6	1	Both	Failed %CV PVT criterion (14% *vs.* limit of 11%)
	24	1	Both	Failed %CV PVT criterion (12% *vs.* limit of 11%)
	27	1	Both	Failed GM PVT criterion (74 *vs.* limit of 72)
Control charts	18	2	1	High geometric mean (49)
Outliers	8	2	1	42
	30	2	2	51

Table III Geometric Mean (GM) and %CV Results for Lot P1

		Apparatus 1	Apparatus 2
	GM	65	36
Variance components (%CV)	Collaborator	5.1%	5.2%
	Experiment	4.6%	5.0%
	Within-experiment	7.6%	5.0%
	Reproducibility	10.2%	8.8%

tailed 0.0027 probability was used, but only the upper control limit was applied. Table II identifies the one set of tablets that was outside the control chart limits. This experiment is identified in Fig. 3.

3. The exclusions of Steps 1 and 2 were applied, and the data were analyzed again using the nested model. These analyses were examined for individual tablet results that were outliers, *i.e.*, that were unusual relative to the other values in the particular experiment. In the two analyses together there were two Studentized residuals greater than 3.0 in magnitude, both for Apparatus 2. The values were 3.9 and 4.3, so those two were dropped as outliers. This corresponds approximately to the 5% critical value for Grubb's test for outliers and, by examination of Fig. 3, identified values that were substantially separated from the remaining values of that experiment. These values are identified in Fig. 3.

Determination of Acceptance Limits

For determination of new PVT acceptance limits, the exclusions of Table II were applied. Table III shows the estimated GM and variance components (as %CV).

Table IV shows the new GM/%CV limits for both the single- and two-stage tests. For Apparatus 2, the limits in Table IV are adjusted from those obtained from the collaborative study as described in the next paragraph. Figs. 4 and 5 show the GM and %CV for each laboratory (combined over each laboratory's two experiments) with the single-stage limits shown as horizontal lines. (For Apparatus 2, the limits are those from the collaborative study, not the adjusted limits of Table IV.) The error bars are 95% confidence intervals based on each laboratory's within-experiment variability and provide an indication of variability in results absent between-experiment and between-laboratory effects.

For Apparatus 2, given the mean trend shown in Fig. 2, we modified the geometric mean limits from the collaborative study by extrapolating according to the observed trend. Fig. 6 shows the data, trend, and corrected single-stage GM acceptance limits for Apparatus 2. The data and trend line are the same as in Fig. 2 with the trend now extrapolated to 80 months after release of Lot P0. The resulting curves for the limits of a single-stage test are shown as dotted curves bracketing the mean curve. The acceptance limits for the geometric mean are taken as correct at the time of the collaborative study and then are extrapolated using the same trend as found for the mean (Fig. 2). The three vertical lines mark the midpoint of data collection from the 2009 collaborative study (43 months), the release date for Lot

Table IV PVT Acceptance Limits for USP Prednisone Tablets Lot P11

Apparatus	Number of vessels	Single stage		Two stage			
				First of two stages		Second of two stages	
		GM	%CV	GM	%CV	GM	%CV
1	6	56–75	10	60–71	7.7	56–75	10
	7						9.8
	8						9.7
	12			na			
	14			na			
2	6	25–41	6.8	27–38	5.1	25–41	6.7
	7		6.7				6.6
	8		6.5				6.4
	12		6.7	na			
	14		6.6	na			

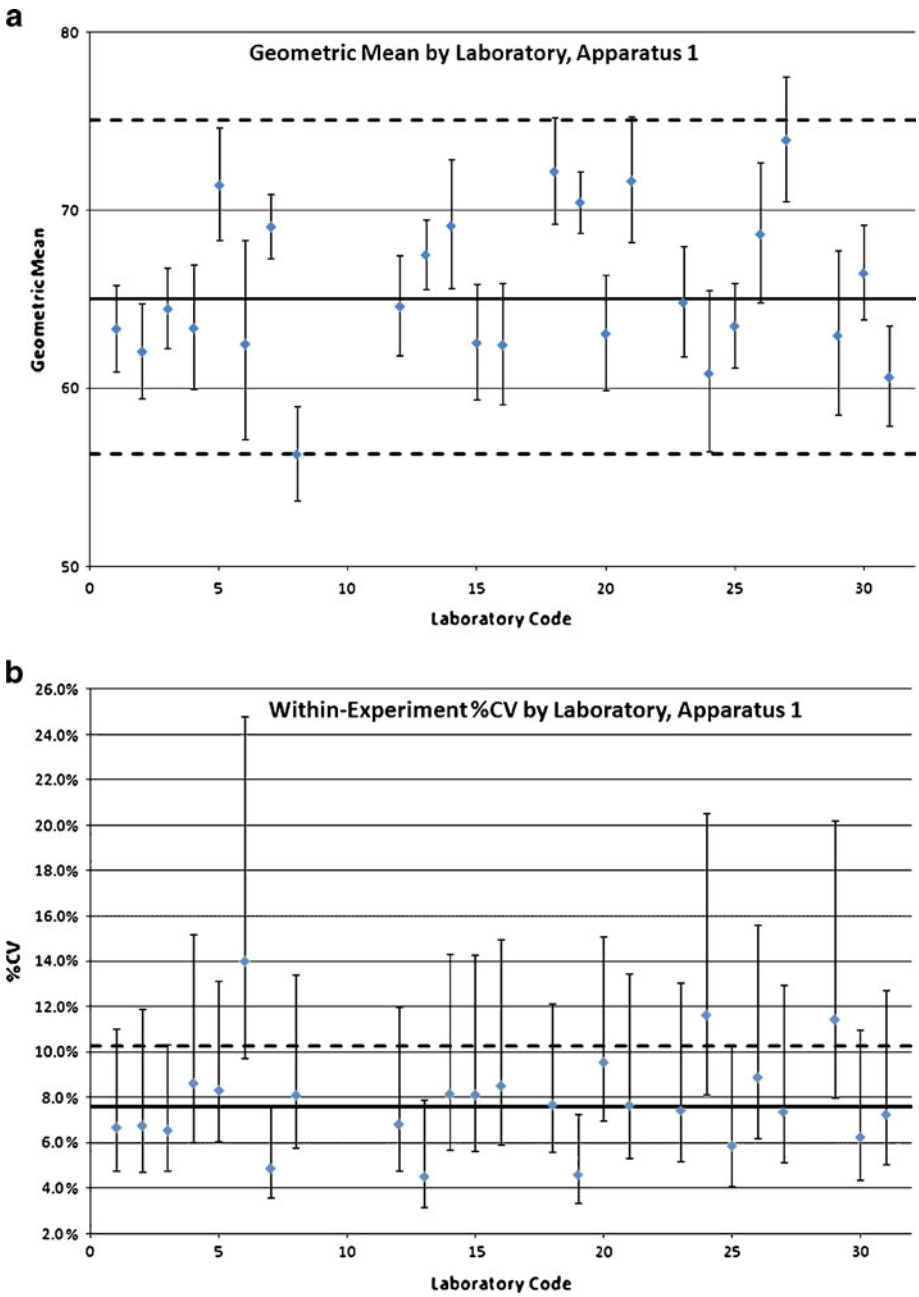

Fig. 4 GM and %CV by Laboratory, Apparatus 1. Error bars are 95% confidence intervals based on each laboratory's position variability. Horizontal dashed lines are the combined value from the collaborative study and the single-stage Lot P1 PVT GM limits for an instrument with six positions. Limits for seven- and eight-position instruments are tighter.

P1 (1 March 2010, 52 months), and two years after release for Lot P1 (28 February 2012, 76 months). The proposed upper limit for GM is adjusted using the upper limit curve to account for the decrease that already happened at the time of P1 release (9 months after the collaborative study), and the lower limit of GM is adjusted using the lower limit curve to account for this trend to the end of Lot P1's shelf life (33 months after the collaborative study). The upper and lower limits were adjusted differently, so laboratories using Lot P1 would be protected against a flattening of the trend.

CONCLUSIONS

USPC conducted a collaborative study to update PVT acceptance limits for Prednisone Tablets RS, now termed Lot P1, and other studies to evaluate the properties of these tablets. We have shown that the results are stable over time in Apparatus 1. In Apparatus 2, there is a trend in the geometric mean of the results but not the variability. In addition, the tablets remain sensitive to two important operational parameters, degassing and vessel dimensions.

The new acceptance limits are for the GM and %CV and thus more directly address the trueness and precision of

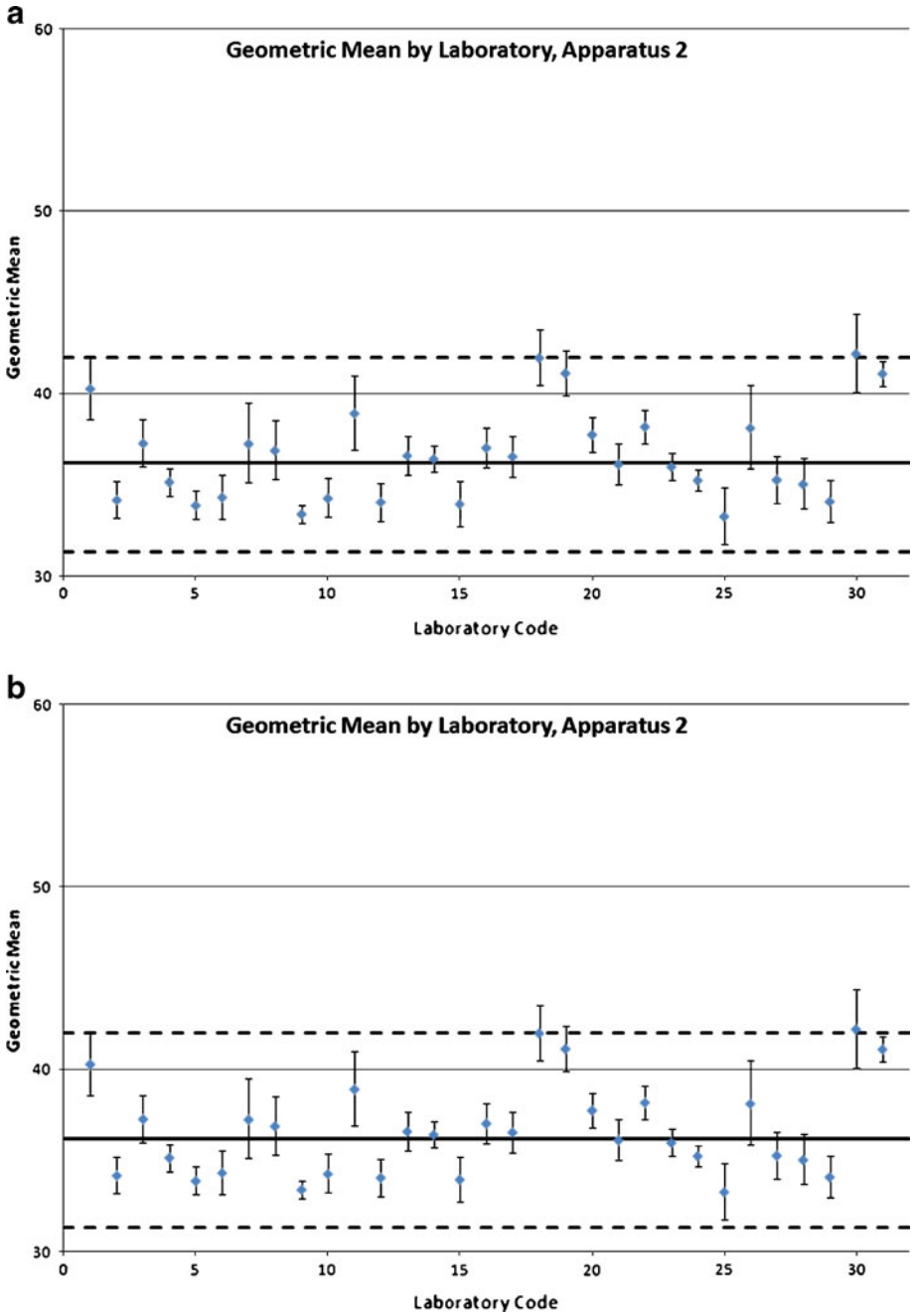

Fig. 5 GM and %CV by Laboratory, Apparatus 2. Error bars are 95% confidence intervals based on each laboratory's between-position variability. Horizontal lines are the combined value from the collaborative study and the single-stage Lot P1 PVT GM limits for an instrument with six positions. Limits for seven- and eight-position instruments are tighter. The limits for the geometric mean are those at the time of the collaborative study.

the laboratory's results for Lot P1 than do earlier limits set for each individual result, as well as bringing USPC into alignment with ISO International Standard 5725. Two notable differences appear when one compares these results to those from the prior collaborative research to establish the PVT limits for Lot P0 (3).

The first difference is that the percent dissolved values for Apparatus 2 are lower than at the time of the previous collaborative study. The percent release of prednisone from the USPC reference material is trending lower with time for Apparatus 2 but not for Apparatus 1. This is presumed to be due to the different hydrodynamic conditions of the two apparatuses and the position of the tablet in the dissolution vessel. In determining the Apparatus 2 GM acceptance limits for Lot P1, we extrapolated this trend and used wider limits than obtained from the collaborative study in order to protect users from false failures to the low side over the two-year expiry period.

The second difference is that there is less variability in the data from this collaborative study, particularly for Apparatus 2. The between-position variability was 8.5% in the prior collaborative study (3) compared to 5.0% in this study. The 5% is more consistent with what USPC found as the between-position variability using Prednisone Tablets

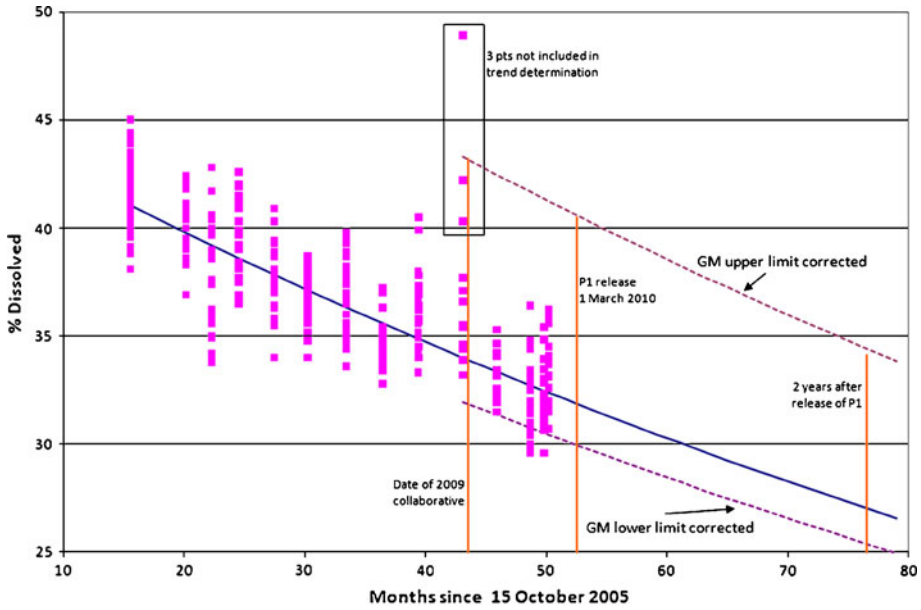

Fig. 6 Adjustment of Geometric Mean (GM) PVT Acceptance Limits for Apparatus 2. The solid curve is the mean trend for the stability data (*squares*), as in Fig. 2, now extrapolated to 80 months. The two dotted curves are the GM limits extrapolated from the time of the collaborative study to 80 months using the same trend as for the mean.

RS in Apparatus 2 (12). For Apparatus 1, the %CV values were similar, namely 8.1% in 2005 and 7.6% in this study. For Apparatus 1, the between-laboratory and between-experiment components were also similar in the two studies. For Apparatus 2, the between-laboratory study component decreased from 8.8% to 5.2%, but the between-experiment component increased from 0.0% to 5.0%, resulting in similar combined contributions from these two components.

Two of the differences between the P1 collaborative study in 2009 and the P0 collaborative study in 2005 were a tighter selection process for laboratories and a requirement that the prior PVT and mechanical calibration results be documented. Mechanical calibration was evaluated using the current <711> specifications, not the somewhat tighter limits of the recent FDA guidance (10). We continue to see substantial between-experiment and between-laboratory variability. Figs. 4 (Apparatus 1) and 5 (Apparatus 2) show the GM and %CV for each laboratory. Data in Figs. 4 and 5 also demonstrate greater inter-laboratory differences in GM than can be accounted for by between-position variability, an indication that differences in inter-laboratory GM differences are not simply randomly due to variations in tablets, assay, and the like. Among the laboratories, all of whose data were used in determining the new limits, one failed the new %CV requirement for Apparatus 1 and three for Apparatus 2. Of these four failures, three had high %CV in their prior PVT. In total, three of the 25 laboratories fail the new %CV requirement for Apparatus 1 and seven of 32 fail the new %CV requirement for Apparatus 2. All three of the laboratories failing Apparatus 1 and four of the seven failing Apparatus 2 had high variability in their prior PVT. This highlights that the prior, per-tablet, criterion was not controlling variability of results. As long as the individual results were within the acceptance limits, it did not matter how different they were. The new %CV criterion now directly controls variability and further supports USPC's decision to change the criterion.

USPC has taken many steps to help laboratories with the PVT test and the transition to the new acceptance criteria. One of these is an online dissolution toolkit that describes procedures for mechanical calibration and the PVT (13). The demonstration that a test assembly is suitable for the dissolution test includes both a demonstration of passing results from the PVT as well as verification of proper operating parameters and component dimensions (mechanical calibration). Careful adherence to mechanical calibration practices is a recognized necessity for dissolution test equipment (4,10). Similarly, the USPC PVT follows the procedures that were required of participants in the collaborative study for Lot P1. The mechanical calibration procedures and recommendations available with the on-line dissolution toolkit go beyond the specifications given in *USP 32* and, although they are not part of the official requirements, can be useful in the dissolution laboratory (13).

Table V Futility Criteria for %CV from First Stage of Two-Stage Test

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

The dissolution toolkit is supplemented by a Web-based calculation tool for the PVT results (13). The procedures used to calculate the GM and %CV from raw dissolution results are given in the RS certificate. The calculation tool allows the calculation of the geometric mean and %CV directly from user input of dissolution results. A total of 14 combinations of apparatuses, test assembly configurations, and choice of single- or two-stage procedures are represented in the calculation tool.

For laboratories that choose to use the two-stage approach, there are conditions where the first-stage %CV results make it impossible to meet the %CV acceptance criteria after the second stage. Recognizing this futility condition allows the laboratory to save the effort of conducting the second stage of testing. If the %CV after the first stage equals or exceeds the value in Table V (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, USPC recommends that this be part of the laboratory's standard operating procedure for this procedure. In general, a laboratory can stop after the first stage if analysts see a problem. However, after any adjustments to equipment, test procedure, *etc.*, the PVT must be restarted again with a new first run.

DISCUSSION

As exemplified by data in this paper, mechanical calibration is a necessary but not sufficient tool for the assessment of dissolution equipment's performance, with the addition of the PVT using independently available reference material adding separate and distinct value. The PVT provides useful information about parameters not amenable to mechanical calibration or that are not identified as requiring control in addition to representing the combination of whatever deviations are left following mechanical calibration. Among the additional parameters are degassing and vessel dimension variability, analyst, and analytical procedure. Prior work (7–9) has shown that vessels, all of which meet <711> specifications, can vary sufficiently to influence the between-position variability and mean of results. With the proper selection of vessels, we see a between-position variability as low as 2% (8), putting an upper limit on the variability that can be attributed to the tablets.

USPC's Prednisone Tablets RS demonstrate reduction in mean rate of release over time in Apparatus 2, but this finding does not alter their value as a means of ensuring the performance of dissolution equipment when applied as part of the USPC performance test. Although this change in performance might not be acceptable in a therapeutic product, the Prednisone Tablet RS is not a therapeutic product but rather an independently prepared reference material with the chemical prednisone part of a specially manufactured matrix. Its change in performance relative to its utility is resolved through periodic collaborative and other studies with adjustment in acceptance criteria. USPC will monitor performance of the USPC Prednisone Tablets RS through these studies and will adjust the acceptance criteria, if needed, at periodic intervals.

Though variability is reduced relative to that seen in the prior (2005) collaborative study, the GM acceptance criteria for acceptable PVT results remain wide due to inter-laboratory variability and, for Apparatus 2, due to the need to allow for the expected change in the mean percent dissolved over the two-year shelf life. The between-position %CV remains constant over time. The move to the geometric mean and %CV criteria brings the acceptance criteria in line with current accepted statistics and provides a more realistic assessment of the system's performance. Sensitivity measures indicate that available Lot P1 continues to identify issues associated with selected test performance parameters. Mechanical calibration alone is not capable of providing this information, nor does it allow assessment of conduct of the dissolution procedure using independently prepared reference material.

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