Systematic Error Associated with Apparatus 2 of the USP Dissolution Test III: Limitations of Calibrators and the USP Suitability Test

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Received April 19, 1982, from the *National Center for Drug Analysis, Food and Drug Administration, St. Louis, MO 63101.* Accepted for publication July 22, 1982.

Abstract □ The calibrator tablets now used in the USP suitability test do not reveal common sources of systematic error associated with Apparatus 2. When the apparatus was operated under conditions near or beyond USP tolerances, changes in the results of the USP calibrators were slight, whereas those of several samples of commercial prednisone tablets were significant. Thus, the USP calibrators and requirements do not guarantee suitability of the equipment for general dissolution testing of drug products.

Keyphrases □ Dissolution—systematic error associated with Apparatus 2 of the USP dissolution test using calibrator tablets □ Calibrator tablets, USP—systematic error associated with Apparatus 2 of the dissolution test □ Apparatus 2—of the USP dissolution test, systematic error using calibrator tablets

The USP provides an Apparatus Suitability Test (1) to ensure that a dissolution apparatus operates satisfactorily and is free from significant extraneous vibration (2). Two official calibrators, both compressed tablets, are available[1] for use in the test. The nondisintegrating calibrator is labeled to contain 300 mg of salicylic acid; the disintegrating calibrator is labeled to contain 50 mg of prednisone. The test conditions for use of the tablets and the ranges within which the results must fall appear in information sheets provided with the calibrators.

Before a given piece of equipment is considered suitable for use as Apparatus 2, it must pass a four-point test. Dissolution results from both calibrators must fall within the established ranges at 50 and 100 rpm. If the equipment fails the test, alignment, speed, vibration, *etc.* should be checked and corrected. If the requirements cannot be met, the equipment is judged unsuitable for use as Apparatus 2 (3). Thus, equipment suitability is determined by the response of the calibrator tablets to variations in the USP test conditions.

Some of the test conditions are defined in terms of numerical tolerances, *e.g.*, the shaft rotation speed is to be maintained within ±4% of a specified value, and the shaft axis is to be positioned not more than 2 mm from the vertical axis of the vessel. Others are defined in absolute terms, *e.g.*, the vessel is cylindrical with a spherical bottom, and the paddle blade forms a section of a circle of specified diameter subtended by parallel chords of specified length. Certain other test conditions are not clearly defined, but rather are to be controlled so that they do not significantly influence the results, *e.g.*, no part of the assembly (vessel, paddle, and variable-speed drive) or the surrounding environment should contribute significant motion, agitation, or vibration beyond that which is due to the smoothly rotating paddle, and dissolved gases are to be removed from the dissolution medium if they change the dissolution results.

Results from commercial prednisone tablets can be influenced by minor variations in equipment alignment (4) and small differences in vessel curvature (5). Both of these conditions may cause systematic error among laboratories. Another possible source of error, recognized in the USP, is the effect of excess gas in the medium.

Two studies (6, 7) indicate that the USP calibrator tablets do not respond to certain variations in test conditions associated with Apparatus 2. Such lack of response normally would lead to the conclusions that the test is rugged, and that similar results for these tablets could be obtained among laboratories. However, the collaborative study results used to derive the acceptance ranges (3) show that similar results were not obtained among the laboratories.

Because the calibrator tablets respond only slightly to variations in test conditions, the purpose of the suitability test is not achieved. Comparisons of the responses of the USP calibrators and certain commercial prednisone tablets to variations in selected test conditions are presented in this paper.

EXPERIMENTAL

Apparatus and Samples—Two analysts, each using a separate commercial apparatus[2], performed the USP suitability test with 50-mg prednisone tablets[1] and 300-mg salicylic acid tablets[1]. A commercial 10-mg prednisone tablet, previously identified as Tablet 2 (5), was studied in a similar manner using the appropriate USP methodology (8).

Each analyst, working independently, adjusted the apparatus to conform to the USP test conditions as closely as practical. One analyst worked with an apparatus that possessed parallel shafts; the other worked with an apparatus known to have two shafts that were not parallel to the other four (4, 5). Although the shaft alignment in the vessels in these two positions differed from the shaft alignment in the vessels in the other four positions, the apparatus could be adjusted to pass the USP requirements.

Six tablets from each of the three samples were tested. A third analyst measured the absorbances of the filtered aliquots, thus minimizing systematic error in this step of the test. These results became a benchmark to which other results were compared; benchmark results were obtained before and after test conditions were varied.

Variations in Test Conditions—Selected test conditions were changed from the USP requirements, one at a time. Six additional tablets from each sample were tested after each change.

Paddle Rotation—The motor drive was operated at least 15 min to allow it to stabilize. The drive was then adjusted to give the desired number of revolutions in 60 (+1, −0) sec by manual count and use of a stopwatch. The rotational speed was again measured after the aliquots were obtained and filtered. In this way the benchmark results were obtained at 50 (± 0.8) and 100 (± 1.6) rpm. For comparison, data were also obtained at 54 (± 0.9) and 108 (+ 3.3, − 1.8) rpm.

[1] USP–NF reference standards (prednisone, Lot F; salicylic acid, Lot G), U.S. Pharmacopeial Convention, Inc., Rockville, MD 20852.

[2] Model 72RL, Hanson Research Corp., Northridge, CA 91324.

0022-3549/83/0800-0910$01.00/0

Table I—Response of USP Nondisintegrating Calibrator Tablets [a] to Changes in Test Conditions [b]

Test Condition [c]	50 rpm [d]				100 rpm [d]			
	Analyst 1		Analyst 2		Analyst 1		Analyst 2	
	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*
Benchmark [e]	15.9	2.3	15.2	2.0	21.0	1.2	21.2	1.1
A	16.6	1.4	16.1	1.7	20.6	0.8	21.0	1.2
B	16.5	1.8	15.6	0.8	19.9	0.6	21.0	0.8
C	19.2	2.1	16.9	2.7	20.0	0.8	20.1	1.0
D	17.2	2.1	17.2	1.2	20.2	0.8	21.2	0.9
E	18.5	3.2	19.3	2.4	21.5	1.2	22.2	0.3
F	18.3	2.7	16.0	1.7	20.2	0.7	20.3	1.8
G	16.1	1.6	14.9	0.7	19.5	1.4	20.6	1.7
H	16.9	1.5	16.6	0.8	23.4	1.8	23.1	1.3
I	15.7	1.6	18.8	3.0	20.4	0.6	20.6	1.4
J	—	—	18.7	1.4	—	—	20.7	1.3
Benchmark [f]	17.0	3.4	16.9	3.1	20.1	1.1	21.5	1.3

[a] Salicylic acid, 300 mg, Lot G. [b] Expressed in percent of label claim; $n = 6$. [c] (A) 54 or 108 rpm; (B) irregular glass vessels; (C) paddle rotating before tablet dropped; (D) vessel axis displaced 2 mm from paddle axis; (E) vessel axis displaced 4 mm from paddle axis; (F) nonvertical shafts (test 1); (G) nonvertical shafts (test 2); (H) medium not deaerated; (I) paddle depth 2.0 cm; (J) probe present throughout test. [d] Except results obtained under test condition A. [e] Obtained before any variation in test conditions. [f] Obtained after variations in test procedures were completed.

Table II—Response of USP Disintegrating Calibrator Tablets [a] to Changes in Test Conditions [b]

Test Condition [c]	50 rpm [d]				100 rpm [d]			
	Analyst 1		Analyst 2		Analyst 1		Analyst 2	
	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*
Benchmark [e]	68.8	1.5	67.2	3.1	76.7	1.2	74.6	1.1
A	71.9	0.7	68.5	1.4	77.0	1.2	76.0	0.8
B	69.1	1.0	64.3	2.9	75.7	2.0	75.4	1.2
C	68.6	3.1	67.4	2.3	77.6	0.8	74.4	1.2
D	67.7	1.9	65.8	1.1	77.6	0.9	74.6	1.1
E	70.4	0.9	68.8	1.2	78.7	1.1	75.9	0.8
F	69.6	1.3	69.2	1.3	77.9	1.5	75.0	1.7
G	69.3	0.7	68.0	1.2	79.6	0.8	75.5	0.9
H	67.3	1.5	64.6	3.3	74.8	1.5	73.4	0.6
I	70.2	1.2	66.6	1.0	76.8	1.3	75.1	0.7
J	—	—	67.5	2.8	—	—	77.1	1.1
Benchmark [f]	69.3	1.4	67.3	1.2	77.6	1.0	75.9	1.2

[a] Prednisone, 50 mg, Lot F. [b] Expressed in percent of label claim; $n = 6$. [c] As in Table I. [d] Except results obtained under test condition A. [e] Obtained before any variation in test conditions. [f] Obtained after variations in test procedures were completed.

Vessels—Six plastic vessels[3] were used by each analyst to obtain the benchmark results. For comparison, one set of irregular glass vessels[4] was used by both analysts. The inside bottom curvatures of these glass vessels did not conform to USP specifications (5).

Tablet Immersion—For benchmark results, each tablet was allowed to sink to the bottom of the vessel before the clutch controlling the paddle rotation was engaged. Results for comparison were obtained with the tablet dropped into the vessel while the paddle was rotating.

Centering of Vessels—The tops of the plastic vessels were centered precisely around the paddle shafts when the benchmark results were obtained, using a specially designed centering tool (9). For comparison, results were obtained with each paddle shaft set either 2 or 4 mm from the center of the top of its vessel. To measure these offsets, an overlay of concentric circles 9.5, 13.5, 17.5, and 21.5 mm in diameter was placed over the centering tool with the innermost circle coinciding with the top of the hole in the centering tool. The tool was placed in the top of one of the centered, rigidly held vessels. The paddle shafts were inverted in the chucks of the dissolution apparatus drive head, and the drive head was repositioned until the paddle shafts were either 2 or 4 mm off-center with respect to the tops of the vessels.

Shaft Verticality—For benchmark conditions, the collars on the stand of the dissolution apparatus were adjusted to 136 mm between the bottom of the drive head and the top of the leveled base of the stand. This distance was chosen because it equals the distance from the top of the stand base to the bottom of the paddles when the paddles are set 2.5 cm above the bottom of the plastic vessels. To facilitate measurements, the paddles were inserted in their inverted (paddle at the top) positions. The drive head was adjusted until a torpedo level (bubble indicators at right angles) placed on the paddle shafts showed that they were vertical. The shafts were then inserted in their normal (paddle down) positions, and the benchmark results were obtained.

Two tests were performed with nonvertical shafts. In the first (test 1), the equipment was misaligned so that each paddle shaft intersected the vertical axis of its vessel at the top of the vessel and was displaced 2 mm from the vertical axis 2.5 cm from the bottom of the vessel. For the second (test 2), the equipment was misaligned so that the paddle shaft axis was displaced 2 mm to the front of the vertical axis of the vessel at the top of the vessel and 2 mm to the rear of the vertical axis 2.5 cm above the bottom of the vessel. Results of both misalignments were compared to the benchmark results.

Deaeration of Media—Water from a commercial deionizer system was mist-sprayed[5] into a 19-liter (5-gallon) glass carboy under vacuum to obtain benchmark results for the prednisone calibrators. For the salicylic acid tablets, the prepared buffer was drawn by vacuum through a 30-mm coarse-porosity glass frit into a 19-liter glass carboy. For comparison, water taken directly from the deionizer system was used for the prednisone samples, and buffer, originally prepared in deionized water and then allowed to equilibrate with the atmosphere at room temperature, was used for the salicylic acid tablets. Both of the latter media released excess gas as bubbles at 37°.

Paddle Depth—The lower edge of the paddle was placed 2.5 cm above the bottom of the vessel as the benchmark and 2.0 cm above the bottom of the vessel for comparison.

Effect of Probes—All aliquots were taken manually with 50-ml syringes fitted with 4-mm o.d. glass tubes cut to lengths that allowed the aliquots to be taken from a standardized position (midway between the top of the medium and the top of the paddle blade and midway between the shaft and the wall of the vessel). For the benchmark condition, the tubes were inserted in the medium only as aliquots were obtained.

To assess the effect of probes, such as those often used with automatic analyzers, a 4-mm o.d. glass tube fitted with a filter tip[6] was placed in the vessel so that the filter was at the standardized position throughout the test. Otherwise, the aliquots were taken as described for the benchmark condition. Only one analyst collected data on the effect of probes in the medium because more thorough studies (10, 11) have been reported on commercial tablets.

Analysis of Commercial Tablets—The two analysts each tested five samples of 5-mg prednisone tablets from four manufacturers. Benchmark results were obtained as described above. Analyst 1 also obtained comparative results with the paddle shafts 2 mm off-center, while analyst 2 obtained comparative results by (*a*) substituting the set of irregular glass vessels for the plastic vessels and (*b*) using the dissolution medium containing excess gas instead of the deaerated dissolution medium.

RESULTS AND DISCUSSION

When possible, test conditions were varied in such a way to theoretically give a higher result: the rotational rate of the paddle was increased, not decreased, and the location of the paddle in the vessel was lower, not higher. The bottom curvature of the irregular glass vessels was flatter than that of a sphere. Any misalignment of the vertical axis of the paddle with that of the vessel tends to raise the results. Because it takes a finite time for motion from the paddle to produce motion in the liquid, dropping the tablet into the vessel with the paddle rotating tends to raise the results.

Whether air dissolved in the dissolution medium will influence test results is difficult to predict. Often, little or no effect is seen; but at times, the effect is dramatic. If the dissolution medium is not deaerated properly, small air bubbles are released from the medium during the test. These bubbles collect on all solid surfaces in contact with the medium, including the tablet or disintegrated tablet particles. Air bubbles adhering to the surface of tablet particles may act as a barrier between the solid drug and the medium. This tends to lower the dissolution results because the drug must contact the medium to dissolve.

Certain tablet products give disintegrated particles with a density such that the particles are lifted from the vessel bottom and circulated by the swirling medium in the absence of air bubbles. With such products the presence of air bubbles tends to lower the dissolution results due to the barrier effect. Furthermore, air bubbles attached to particles may synchronize the particle's motion with that of the medium; in this case, the

[3] Eli Lilly and Co., Indianapolis, IN 46206.
[4] Kimble Div., Owens-Illinois, Inc., Vineland, NJ 08360.
[5] Taken from a three-spray nozzle, available from Fogg-It Nozzle Co., San Francisco, CA 94116.
[6] Centaur Chemical Co., Stamford, CT 06902.

Table III—Response of Tablet 2 [a] to Changes in Test Conditions [b]

Test Condition [c]	50 rpm [d]				100 rpm [d]			
	Analyst 1		Analyst 2		Analyst 1		Analyst 2	
	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*
Benchmark [e]	37.9	3.0	36.2	5.0	79.8	3.1	80.9	6.2
A	41.9	3.0	39.7	5.4	83.6	1.6	82.8	8.3
B	34.8	1.8	35.4	2.1	86.5	5.2	90.6	4.0
C	39.3	1.9	38.8	3.0	78.2	3.7	78.5	6.1
D	40.2	4.0	41.6	4.8	86.8	4.1	88.5	1.7
E	45.7	3.1	45.7	3.3	92.8	1.7	90.3	2.1
F	37.3	4.5	34.9	3.2	78.8	8.2	76.6	7.6
G	37.6	4.6	39.5	5.7	81.6	8.2	80.2	6.3
H	83.0	4.2	83.2	3.9	96.0	1.7	96.4	0.8
I	37.2	2.0	34.6	4.0	80.9	3.9	80.8	5.8
J	—	—	41.2	4.2	—	—	90.9	2.8
Benchmark [f]	34.9	2.5	34.3	5.1	78.2	2.3	75.4	8.0

[a] Prednisone, 10 mg. [b] Expressed as percent of label claim; $n = 6$. [c] As in Table I. [d] Except results obtained under test condition A. [e] Obtained before any variation in test conditions. [f] Obtained after variations in test procedures were completed.

concentration gradients near the particles could increase, also lowering the dissolution results.

Other tablet products disintegrate into particles of sufficient density to collect in a compact, cone-shaped mass on the bottom of the vessel in a region of relatively low liquid agitation. If the density of the tablet particles is changed sufficiently by the presence of air bubbles, the aggregate of particles on the vessel bottom is disrupted and more particles are lifted into regions of higher liquid agitation. Considered alone, this effect raises the dissolution results because more particles are brought into contact with more liquid in a given time. In practice, however, the net result of this effect plus the barrier effect is observed for such products.

The mean results of the USP calibrator tablets change only slightly with variations in individual test conditions (Tables I and II). If a variation in test conditions truly affects the dissolution behavior of these tablets, a bias will be present in the results at both 50 and 100 rpm. Statistical techniques suggested by Steiner (12) were used to analyze the mean results.

The means obtained by each analyst at each rotational rate were ranked from low to high, without the results obtained when probes were present in the dissolution medium. The ranks of all mean results obtained under the particular test conditions (specified in Tables I and II) were summed. The rank sums were then compared with values representing upper and lower limits that would not be exceeded by chance at the 95% confidence level.

When the means obtained from the salicylic acid tablets (Table I) were analyzed by this technique, it was found that a small upward bias may have existed in the results when the USP tolerance for centering was doubled (test variation E). The statistical test gave a borderline result at the 95% confidence level. The means obtained by test variation E were removed, and the means remaining in the table were ranked a second time. The remaining test variations did not give a consistent bias to the results. Individual means were then tested for bias. The means obtained by test variation H at 100 rpm were found to be significantly high at the 95% confidence level. Thus, air bubbles accumulating on the tablets produced a small bias in the results at 100 rpm, but not at 50 rpm.

When the means obtained from the USP disintegrating calibrator tablets (Table II) were ranked and the ranks were summed across the table, test variation H was found to produce a downward bias. Thus, air bubbles accumulating on these tablets lower the dissolution results. After the means from test variation H were removed, no consistent bias was found for the other test variations. No individual means were found to contain a bias significant at the 95% confidence level.

The means obtained from Tablet 2 (Table III) were analyzed in a similar manner. The means obtained under the last benchmark conditions were found to have a downward bias, and test variation H was found to produce an upward bias. After these means were removed, test variation E was found to produce an upward bias, test variation D produced a high bias with borderline significance at the 95% confidence level, and test variation A produced a high bias. No consistent bias was found for the remaining means obtained under the first benchmark conditions and test variations B, C, F, G, and I. When these means were analyzed individually, the two means obtained from test condition B at 100 rpm were found to be significantly high at the 95% confidence level. Thus, a bias is produced in the results from Tablet 2 by not deaerating the medium, by not centering the paddles in the vessels, by doubling the USP tolerance for rotational rate of the paddle, and, at 100 rpm, by using glass vessels with flattened bottom curvatures. The magnitude of the bias is large when there is excess gas present in the medium. The magnitude of the bias is noticeable when the USP tolerance for centering is doubled and, at 100 rpm, when the paddles are shifted 2 mm from the vessel centers. The bias from the glass vessels is noticeable at 100 rpm.

Probes, used in many laboratories to take aliquots automatically, can influence the dissolution results of tablets (10, 11). The USP calibrator tablets do not respond noticeably to changes in the hydrodynamics of the test generated by the probes (Tables I and II).

Five samples of 5-mg prednisone tablets from four manufacturers were subjected to selected changes in test conditions (Table IV). Analyst 1 used an apparatus previously described (4) and discussed (5). Because the paddle shafts in positions 4 and 6 were not parallel to the other four shafts, tablets from each of the samples gave higher results in these two positions. All shafts in the apparatus used by analyst 2 were parallel. This difference in equipment is the major cause of the differences between the benchmark results collected by the two analysts. The response to changes in test conditions is considerably greater for the commercial tablets than for the calibrator tablets. These commercial tablets fail the USP dissolution test when the test is performed under benchmark conditions, but may easily pass the test when the conditions are only slightly altered.

The official acceptance ranges for the USP calibrator tablets are based on results of collaborative studies (Table V) that involved 20 laboratories (3). Two independent studies of the 50-mg prednisone tablets at 50 rpm have also been reported—one by 5 (6) and the other by 11 FDA laboratories (13).

The official ranges show considerable overlap: the equipment could give identical results at 50 and 100 rpm and yet pass the requirements. This paradox arises from the large systematic errors of unknown origin among the 20 collaborating laboratories. However, only a small part of the wide spread in collaborative results can be ascribed to malfunctioning equipment (Tables I and II).

The official ranges are much too wide. According to the USP calibrators and ranges, the equipment used to collect the data in Tables I–IV is suitable for use, even when the measurable official tolerances (rotation and geometry) are exceeded. Narrowing the official calibrator ranges will not help, however, because the USP calibrators do not respond to the variables of interest (Tables I and II).

Tablet 2 has been used in several FDA laboratories as a performance standard for Apparatus 2, complementing, but not replacing, the USP calibrators. The acceptance ranges for Tablet 2 (Table V) were derived from a collaborative study by 11 FDA laboratories (13). Although Tablet 2 shows excellent sensitivity to excess gas in the dissolution medium, it does not respond adequately to irregularities in vessel curvature or to equipment misalignment. Nevertheless, Tablet 2 often has revealed subtle differences among sets of dissolution equipment that appeared equivalent when tested with the USP calibrators.

Roles of Disintegration and Density—Tablets that do not disintegrate during the test usually show little response to malfunctioning equipment or excess gas in the medium. Tablets that disintegrate within 2–3 min and give disintegrated particles that are lifted and circulated throughout the medium are usually immune to minor variations in equipment alignment and vessel curvature. Tablets that disintegrate within 2–3 min into granules that remain on the vessel bottom are likely to respond to such minor variations and, thus, are candidates as calibrators for the test.

Tablet Position Effect—The behavior of a tablet that disintegrates after 5–7 min is influenced by its position in the vessel[7]. If such a tablet settles at the center of the vessel, it will take longer to disintegrate and will exhibit a slower dissolution rate than a similar tablet that settles some distance away from the center. The latter tablet will disintegrate faster, and the disintegrated tablet material will be pulled toward the center by the circular liquid flow generated by the rotating paddle. For prednisone tablets of this nature, differences of 10–20% of label claim are commonly seen among the dissolution results of individual tablets. If the tablets settle at widely different locations in the dissolution vessels, the mean result will be higher than it should be and the standard deviation will be large. The wide range of results usually is blamed on the "inherent standard deviation" of the tablets when, in fact, it is due to the scattered positions of the tablets at the start of the test. The two samples of tablets from manufacturer B (Table IV) take from 10–15 min to disintegrate and exhibit this position effect. Ideally such tablets should be positioned at

[7] This effect has also been observed in Food and Drug Administration laboratories in Chicago, Ill., and Winchester, Mass.

Table IV—Response of Commercial 5-mg Prednisone Tablets to Changes in Test Conditions [a]

Condition [c]	Manufacturer A Mean	A SD	B_1 [b] Mean	B_1 SD	B_2 Mean	B_2 SD	C Mean	C SD	D Mean	D SD
Benchmark [d]	68.4	12.2	69.2	16.3	77.2	14.7	75.3	7.5	79.7	5.4
Benchmark [e]	70.8	5.3	64.6	9.0	71.0	7.2	74.0	4.2	76.4	4.3
B [e]	76.3	8.0	77.6	13.3	80.3	11.9	82.5	10.7	82.5	6.3
D [d]	88.0	3.5	94.2	2.3	95.8	2.9	90.4	3.0	87.0	3.2
H [e]	98.9	1.4	97.2	1.7	95.7	2.1	97.3	1.6	95.5	2.7

[a] Expressed in percent of label claim; $n = 6$. [b] Two different lots from manufacturer B were used. [c] As in Table I. [d] Performed by Analyst 1. [e] Performed by Analyst 2.

the bottom of the vessel at the start of each test. Tablets whose results depend on their initial position in the vessel should not be considered as potential calibrators.

Role of Calibrators—The ideal calibrator is easily defined, but has yet to be found. It should warn of incorrect shaft-rotation speed, equipment misalignment, irregularities in vessel curvature, *etc.* The calibrator results must leave no doubt about equipment suitability. A reproducible way to manufacture the calibrator must exist so that it may be distributed widely. These requirements will not soon be met. A simple suitability test for correct equipment setup is highly desirable, but its benefits may be outweighed by the expense of developing and manufacturing the required calibrator.

Meanwhile, most of the requirements for suitability of equipment can be met without using calibrator tablets. Alignment of equipment can be ensured by careful measurement with centering tools, calipers, and bubble levels. Uniform vessels are available. Control of shaft-rotation speed and temperature is trivial. Drug manufacturers can easily test whether deaerating the media influences the results for their products.

CONCLUSIONS

Large systematic errors existed among the laboratories that contributed the data from which the USP acceptance ranges for the official calibrators were derived. The sources of these errors are unknown; however, the USP calibrators do not warn of common equipment malfunctions. Thus, the USP suitability test cannot ensure correct equipment operation.

The general chapter on dissolution testing in the USP recognizes many of the test conditions that require control and gives an idealized concept of how the test is to be conducted. Unfortunately, control of equipment tolerances is not well defined in some cases and not fully adequate in others. The effect of changes in some of these equipment conditions on the dissolution results obtained from certain commercial tablets has been demonstrated.

Although equipment alignment and shaft-rotation speed may be controlled with simple measurements, a calibrator tablet is very useful when checking for test conditions that are difficult to measure (*e.g.*, excess gas) or that require sophisticated equipment (*e.g.*, vibration). One cannot rely totally on calibrator tablets to establish that the dissolution test conditions remain unchanged from day to day unless these requirements are met: (*a*) the tablets must respond to changes in critical test conditions, (*b*) the tablet response must be measured under rigidly controlled and well-defined test conditions, and (*c*) an acceptance range must be established within which variations in results due to minor fluctuations in test conditions can safely be ignored.

Table V—Acceptance Ranges for Tablets Used in the Apparatus 2 Suitability Test

Tablet	rpm	Acceptable Range of Means [a]	Maximum Acceptable *SD* [a]
Salicylic acid	50	14.1–22.5	3.7
Lot G [b]	100	17.6–30.0	3.7
Prednisone, 50 mg	50	56.6–77.0	4.5
Lot F [b]	100	67.9–84.3	3.2
Lot F [c]	50	63.1–73.2	3.3
Lot F [d]	50	62.4–69.8	4.1
Tablet 2 [d]	50	32.5–45.3	5.9

[a] Expressed in percent of label claim; $n = 6$. [b] Basis for official USP values, derived from results collected by 20 Pharmaceutical Manufacturers Association laboratories (3). [c] Derived from results collected by 5 FDA laboratories (6). [d] Derived from results collected by 11 FDA laboratories (13).

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ACKNOWLEDGMENTS

The authors thank John C. Black for constructing the overlay of concentric circles.