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History of Dissolution Calibration

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The pharmaceutical industry has been officially performing dissolution testing for a quarter of a century. For the last fifteen years, those tests have been conducted using equipment that had to meet a standardized set of prerequisite performance criteria. Since that time, those established performance criteria have not changed. We may find value in reviewing the history of dissolution testing in general and the background of the equipment calibration criteria in particular to determine if those same criteria will serve us, and the science of dissolution, adequately in the future.

The etiology of our current systems may be divided roughly into three parts, for the sake of discussion:

- *the beginnings, where, ultimately, the stage was set for the need for standardization.*
- *the period of formalization, which represented the transition from a more or less uncontrolled environment to one in which standards were universally established.*
- *the process of optimization, during which we have matured in our understanding of variables and our abilities to determine "true" (or, at least, reproducible) dissolution rates.*

The Beginnings

While we may think of dissolution as a contemporary consideration, Bernard Proctor recognized that "pill" dissolution was a prerequisite for drug absorption in the late 1800's. As early as 1897, studies and mathematical characterization of dissolution rates of poorly soluble chemicals were published. During the 1930's, experiments with *in vitro/in vivo* correlations using disintegration were reported. These led to disintegration testing becoming an official test in the USP in the 1950's. In the early 1950's, correlations were postulated between the dissolution of aspirin in the gut and analgesic effect. Eight years later, that *in vivo/in vitro* postulation was confirmed using amphetamine. The Kefauver-Harris Drug Amendments passed the U.S. Congress in 1962 to ensure drug effectiveness, as well as safety.

Later in the sixties, a joint panel on physiologic availability was formed by the USP and the NF. This Joint Panel evaluated mechanisms to help ensure drug effectiveness. Their recommendation set the stage for officially sanctioned dissolution testing for oral dosages. They concluded:

- Testing to demonstrate the rate at which active ingredients dissolved from dosage forms would be needed.
- The rotating basket method would be the most suitable standard method, based on the results of non-disintegrating salicylic acid tablets.
- Testing of individual dosage units would be necessary to ensure uniformity of performance within a batch. (This recommendation would become a key element in the subsequent development of standardized tests.)
- "Calibrator" tablets would not be necessary.

Formalization

As a result of the activities of the sixties, the USP and NF published official dissolution tests for twelve monographs in 1970. All of these tests followed the recommendations of the joint panel and used the rotating basket apparatus.

Almost immediately, scientists in all arenas began to report problems with lack of reproducibility in dissolution results. These differences were not only from lab to lab, but also from apparatus to apparatus within the same laboratories. The FDA labs (NCDA; now DDA) found that the specifications in the initial official dissolution tests in the compendia could not be effectively enforced

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due to this, seemingly, inherent variability in the test method. Both the USP and the FDA began to stress the need for standardization in dissolution testing. Some of the effects of vibration and apparatus geometry in the "first generation" equipment, as well as effects of media variables, were beginning to be identified and reported.

To begin to address the issue of non-reproducibility, the USP Committee of Revision Subcommittee on General Chapters was charged, in 1975, with developing appropriate "calibrator" tablets. That group established two suitable apparatuses, the rotating basket and the rotating paddle. A collaborative study involving industry, the FDA, and the USP, to evaluate potential calibrator tablets was coordinated through the PMA (now PhRMA).

During this time, the FDA published several articles describing their opinion of the importance of bioequivalency of formulations. These articles stressed the value of in vitro testing to ensure that bioequivalency. Also, the USP published its position on a general dissolution requirement in 1977. That paper signaled the USP's intent to have a defined dissolution test and requirement for all oral solid dosage forms. The FDA's NCDA, culminating several years of extensive work on dissolution variables, published "Guidelines for Dissolution Testing," which was and still is the benchmark paper defining the major variables in dissolution and how to control them.

In 1978, the USP published the results of the PMA's collaborative study to establish "calibrator" tablets. That study evaluated one non-disintegrating tablet (salicylic acid 300 mg tablets) and two disintegrating tablets (prednisone 50 mg tablets and nitrofurantoin 100 mg tablets). The collaborative group determined that the nitrofurantoin tablets dissolved too rapidly to be an ideal calibrator and only recommended prednisone and salicylic acid.

The design of that first collaborative study gives evidence of some of the original rationale for "calibrators." The basket apparatus was evaluated at 50, 100, and 150 rpm, while the paddle apparatus was evaluated at only 50 and 100 rpm. These multiple speeds were evaluated to cover the potential range of use of the equipment. The collaborative group dropped the 150 rpm speed to simplify use of the calibrators. The original collaborative used profile sampling at 15, 30, 45, and 60 minute intervals, but the PMA committee recommended the 30 minute time period for routine use.

Statistical analyses were performed as the basis for establishing the specifications for the new calibrator lots. Outlier tests were used to ensure that the specifications for the calibrator lots were based on results from laboratories with the "best" practices. Laboratories were omitted from the calculation of acceptability limits if their within-lab standard deviation was outside of the three sigma limits or if the mean of their results was outside of the two sigma limits (for each test condition).

The recommended acceptance criteria for the proposed calibrator lots was the range calculated as the overall mean from the collaborative plus or minus two times Sx, where Sx is defined as the square root of [the between lab variation] plus [the within-lab variation divided by six]. The PMA recommended that the average and standard deviation (of the six calibrator tablets tested at each condition) be used as the acceptance criteria. Both the FDA and USP felt that the proposed ranges were too wide to use the average, but they would accept the proposed criteria if applied to each individual tablet.

Subsequently, in 1978, the USP established and issued the first official reference standard calibrator tablets. All dissolution equipment used to perform official dissolution tests would now have to meet the compendial calibration requirements, for the type apparatus used, before the results could be considered valid. To meet the USP criteria, each type of apparatus would have to meet the specifi-

cations for each of six tablets, for both the disintegrating and non-disintegrating types, at both 50 and 100 rpm. The USP did not define a requalification frequency, leaving it up to the individual laboratories to recalibrate at an interval that ensured that an apparatus remained within specifications.

The perspectives on the reasons for and role of the calibrators were not—and perhaps still are not—universally the same among all of the institutions in this process. While differences existed among individual players, opinions could be generally characterized as follows:

- The USP felt that the primary reason for calibrators was to control vibration. They generally thought that other variables should be controlled by mechanical measurements.
- The industry and the PMA committee viewed the calibrators as an overall "system suitability" test.
- The FDA/NCDA mostly viewed the calibrators as a general apparatus suitability test and as a test for dissolved gases. However, the NCDA felt that the USP calibrators were not adequate to assess dissolved gases and some types of misalignment.

Because of its opinion of the USP calibrators, the NCDA developed its own internal calibrator lot of prednisone 10 mg tablets, which it identified as "NCDA2." However, this material was from a commercial lot that was removed from the market. It was not available in quantities sufficient to be considered as a sustainable industry standard.

Maturation — The Process of Optimization

The "maturation" of dissolution calibration is certainly a process and not a goal that we have achieved. Many of the initial approaches have remained essentially unchanged. By agreement, all lots of USP calibrators have been qualified by PMA (PhRMA) coordinated collaborative studies. These studies have been as broad-based as possible and normally included participants from the FDA and USP in addition to the industry members. No significant changes in the statistical analyses used to derive the calibrator specifications from the collaborative data have been made since the original study.

Usage of the calibrators was limited in the early years, because there were relatively few official dissolution tests during that period. During the mid-80's, consumption of the calibrator lots increased significantly. Since then, a new lot normally has been required every two to three years, based solely on exhaustion of supply. Six lots of prednisone tablets and eight lots of salicylic acid tablets have been qualified as official since the program began (Tables 1 & 2).

Table 1
Prednisone Calibrators Data History

USP Lot	Date Issued
F	9/78
G	3/84
H	3/87
I12/89	
J	10/91
K	5/94

Table 2
Salicylic Acid Calibrators

USP Lot	Date Issued
F	9/78
G	10/81
H	3/84
I	4/87
J	9/89
K	9/91
L	5/94
m	1/95

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Data History

A natural and legitimate question for the calibrator program is "How have we improved over time?" Assuming (and that is all we can do) that the product lots are relatively consistent in terms of their within-lot dissolution uniformity and assuming that the laboratories are improving their dissolution expertise, we should expect to see a narrowing of the specification ranges resulting from subsequent collaborative studies. Generally, that is the trend that is observed. However, there are some exceptions.

Prednisone Basket 50 rpm

The first prednisone lot (Lot F) appeared to dissolve atypically faster than subsequent lots. We do not know if that was intrinsic to the product or a result of laboratory variables. Otherwise, this test condition demonstrates a progressively smaller span between the minimum and maximum specification values with each collaborative study (Table 3).

Table 3
Prednisone Basket 50 RPM

	Range [1]	Span [2]	% Range Max [3]	Change [4]
Lot F	21 - 49	28	57	—
Lot G	2 - 26	24	92	-4
Lot H	3 - 21	18	86	-6
Lot I	7 - 23	16	70	-2
Lot J	6 - 23	17	74	[+1]
Lot K	7 - 20	13	65	-4

(1) Official specification range for this lot of USP calibrator tablets with this apparatus and speed
(2) The difference between the minimum and maximum range values.
(3) The span expressed as a percentage of the maximum of the range specification.
(4) The change in the span (2) from the previous lot.

Prednisone Basket 100 rpm

As those who have been closely involved with the collaborative process might have expected, the prednisone results with the basket at 100 rpm fail to show a continuous improvement. A significant aberration occurred with Lot I. The trend reversed again with Lot K, although to a lesser extent. Again, we do not understand the reasons for this phenomenon, but the collaborative study for Lot I clearly demonstrated a lot of lab to lab variability (Table 4).

Table 4
Prednisone Basket 100 RPM

	Range	Span	% Range Max	Change
Lot F	49-81	32	40	—
Lot G	29-58	29	50	-3
Lot H	30-50	20	40	-9
Lot I	28-62	34	55	[+14]
Lot J	43-63	20	38	-14
Lot K	36-60	24	40	[+4]

Prednisone Paddle 50 rpm

The ranges and spans for this condition have shown gradual but systematic improvement. The data suggests that we, indeed, are optimizing this test parameter (Table 5).

Table 5
Prednisone Paddle 50 RPM

	Range	Span	% Range Max	Change
Lot F	51-77	26	34	—
Lot G	33-51	18	35	-8
Lot H	31-49	18	37	0
Lot I	34-53	19	36	-9
Lot J	46-59	13	22	-6
Lot K	41-54	13	24	0

Prednisone Paddle 100 rpm

While the data for this condition suggests optimization over the last several collaboratives, an interesting phenomenon is apparent in the nature of the ranges. Notice that the upper speci-

fication is essentially the same over all but the first lot. The significant variation in range span over the sequence of official lots, especially noticeable in Lot H, is produced almost entirely by fluctuation in the lower end of the range. This suggests that a test variable has been brought under control, but we have no direct evidence of which variable that might have been (Table 6).

Table 6
Prednisone Paddle 100 RPM

	Range	Span	% Range Max	Change
Lot F	68-85	17	20	—
Lot G	48-67	19	28	+2
Lot H	41-64	23	36	+4
Lot I	50-66	16	24	-7
Lot J	58-69	11	16	-5
Lot K	57-66	9	14	-2

Not only has the 100 rpm basket test parameter shown the least improvement over time, it almost always has shown the largest absolute span of specification range of any of the test parameters for any of the tablet lots.

An interesting phenomenon for the 50 rpm basket test parameter is that, despite the apparent absolute improvement in specification range span over time, the relative span, expressed as a percentage of the specification range maximum, is dramatically higher than for any other collaborative test condition.

Salicylic Acid Basket 50 rpm

This condition seems to have been optimized. The collaborative process is unlikely to recommend a range more narrow than five percent absolute span (Table 7).

Table 7
Salicylic Acid Basket 50 RPM

	Range	Span	% Range Max	Change
Lot F	13-19	6	32	—
Lot G	13-22	9	41	+3
Lot H	11-20	9	45	0
Lot I	14-22	8	36	-1
Lot J	14-20	6	30	-2
Lot K	14-21	7	33	[+1]
Lot L	15-20	5	25	-2
Lot M	15-20	5	25	0

Salicylic Acid Basket 100 rpm

Likewise, the specification range of this calibration condition may be approaching the practical limits of the test method (Table 8).

Table 8
Salicylic Acid Basket 100 RPM

	Range	Span	% Range Max	Change
Lot F	23-31	8	26	—
Lot G	23-30	7	23	-1
Lot H	20-30	10	33	[+3]
Lot I	21-32	11	34	[+1]
Lot J	22-30	8	27	-3
Lot K	23-29	6	21	-2
Lot L	23-30	7	23	[+1]
Lot M	23-29	6	21	-1

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Salicylic Acid Paddle 50 rpm

While the range span probably is not as narrow as it could be, the results have been amazingly consistent over time. Given that the equipment and practice have improved since the inception of the collaborative process, this may suggest that this test condition is not adequately responsive to test variables (Table 9).

Table 9
Salicylic Acid Paddle 50 RPM

	Range	Span	% Range Max	Change
Lot F	15-24	9	38	—
Lot G	14-23	9	39	0
Lot H	13-23	10	44	[+1]
Lot I	12-22	10	46	0
Lot J	12-22	10	46	0
Lot K	13-22	9	41	-1
Lot L	13-22	9	41	0
Lot M	12-23	11	48	[+2]

Salicylic Acid Paddle 100 rpm

The span of results has gradually, but steadily, narrowed over time. Significant improvement in this test parameter is unlikely (Table 10).

Table 10
Salicylic Acid Paddle 100 RPM

	Range	Span	% Range Max	Change
Lot F	18-36	18	50	—
Lot G	17-30	13	43	-5
Lot H	18-31	13	42	0
Lot I	18-28	10	36	-3
Lot J	17-27	10	37	0
Lot K	16-27	11	41	[+1]
Lot L	16-26	10	39	-1
Lot M	17-25	8	32	-2

Interestingly, the basket yields significantly tighter specification ranges than the paddle for salicylic acid, and it shows some improvement over time. The paddle at 100 rpm showed a dramatically higher span in the first official lots. This suggests that this condition, unlike 50 rpm, may have been responsive to a test variable that was subsequently better controlled.

Issues for the Future

In many respects, the future is now—today. The goal of the calibration program is to ensure the universal reproducibility of dissolution results. We presently have essentially the same calibration criteria for dissolution testing that we established over 15 years ago. While those criteria have aided tremendously in stimulating improvements and standardization in both equipment and technique, valid questions are being asked about the appropriateness of current calibrators and the need for testing four conditions to qualify each type of apparatus. These questions are being driven both by science and economics. Since starting in an era when we understood relatively little about variables that influenced dissolution results, we now have accumulated much data, experience, and knowledge, which we must use in a thorough reevaluation of our calibration process.

- We must determine what role the calibrator tablets should play in standardizing the dissolution test. There is evidence that at least some of the test conditions are immune to many of the test variables and, therefore, provide no value in ensuring "system suitability." Should we continue to try to use a calibrator tablet for overall system suitability assessment or should they be used to control only specific variables that cannot be controlled or monitored in any other way? What characteristics should future calibrator tablets have?

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- How many test conditions should be required to fulfill these newly defined functions. Can they be done with less than four? With one? None?
- What changes will be necessary in the "mechanical" calibrations and the operational tolerances for dissolution equipment? If we understand more now and if equipment is better engineered and built now, why shouldn't we have more demanding criteria for the variables that we can measure directly?

The incentives to make these reassessments are real. The interest and momentum already exist. We need to provide the leadership to focus that energy in a thoughtful and constructive "reinvention" of the best way to ensure accurate, reproducible, and meaningful dissolution test results. Participation in this process by the FDA, the USP, dissolution equipment manufacturers, and the pharmaceutical industry will be essential to ensure that we develop the best overall approach.