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EVALUATION OF THE PERFORMANCE OF PREDNISONE AND SALICYLIC ACID USP DISSOLUTION CALIBRATORS

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Introduction

The testing of *in vitro* drug release profiles from various dosage forms is common practice in pharmaceutical research and quality assurance. Dissolution testing is of paramount significance in routine quality control and should hence be comprised of precise, accurate and robust procedures. USP furnishes explicit guidelines for dissolution testing apparatuses in compliance with compendial standards as described in *Dissolution* <711> General Chapter *Apparatus Suitability Test.* USP requires two dissolution calibrators; (i) Prednisone tablets (disintegrating type) and (ii) Salicylic acid tablets (nondisintegrating type) for use in calibration of dissolution testing apparatus. Acceptable limits of drug release (at the 30 minute sampling time) are provided with the two calibrator tablets for apparatuses 1 and 2 at eight different apparatus/speed settings. The International Pharmaceutical Federation (FIP) is currently working to provide similar suitability criteria for the flow-thru-cell dissolution apparatus (Apparatus 4).

In an effort to develop a broad-based database on the performance of the existing lots of USP dissolution calibrators and evaluate future lots of calibrators, USP requested its calibration customers worldwide to provide data describing the performance of Prednisone (Lot J) and Salicylic acid (Lot K) calibrators. Information on the failure of calibrators and the actions taken by the customers in establishing the cause of the failure were of keen interest to USP. This database would help USP in evaluating the performance of these lots and address areas of potential concern. The main objectives of this study were:

1. Compilation of the responses to USP Dissolution Calibrator Data Survey in the form of a database to facilitate convenient data analysis.

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2. Evaluation and analysis of the database to extract information about the performance of dissolution calibrators.

3. Discussion of typical observations and review of possible conclusions.

Data compilation and analysis

The request for data by USP was made in the last week of January, 1994. March 15, 1994 was set as the deadline for responses. A total of 445 requests were made with 371 requests to the United States, Puerto Rico and U.S. territories, Canada and Mexico. The remaining requests were made to other worldwide customers.

The database was developed in Microsoft Excel (Version 5.0). All computations reported here were performed on an IBM/386 personal computer with enhanced memory. The, software used in the computations was Microsoft Excel (Version 5.0) operating in Microsoft Windows (Version 3.1). All programming was performed in the Visual Basic programming language offered in MS Excel. Functions and procedures were developed to accomplish various computational, sorting and formatting tasks.

The data compilation for this study was accomplished through a retrospective survey and hence, suffers from the natural and inherent shortcomings of any survey. Biases involved in the responses based on specific or particular experiences of certain respondents may not be completely eliminated. Also, the possibility of a very large number of failures from a certain respondent skewing the entire database cannot be ruled out.

RESULTS

Compilation of the database

Of the 445 survey requests sent out by USP (survey) approximately 80 responses gave pertinent information. The response rate to the survey was close to 18%. These 80 responses were examined on basis of the information provided regarding source, country, apparatus, RPM, calibrator. Responses were received from all the five continents. However, the majority of the data came from North America and Western Europe. The developed database consisted of a total 2981 runs (each run of six tablets i.e. 2981 x 6 = 17,886 calibrator tablets) including both calibrators. Data from a few sources were not included as the pertinent information such as percentage dissolved at the end of one-half hour was not provided.

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Failure information

In evaluating the performance of USP dissolution calibrators the failure rate of each calibrator is a statistic of great significance. Apparent percentage failure rates were computed for each calibrator using the global data, US data and non-US data. The failures were categorized into calibrator tablet failures, calibrator run failures (see Tables 1 and 2).

To indicate the measure of the variability in the percentage drug dissolved falling within acceptable limits, the ranges of relative standard deviation (RSD) or the coefficients of variation (CV) are shown in Table 3. These RSD ranges were computed only for data which showed compliance with the compendial requirements for Apparatus Suitability Test. These computations were performed for all calibrator/apparatus/speed combinations.

Time-trend analysis

To investigate trends in the mean dissolution percentages with time, the mean percentage dissolved was plotted on a monthly basis over the entire period for which data was available. Similar plots were also generated for the RSD. This exercise was repeated for all calibrator/apparatus/speed combinations. The highest relative standard deviation (RSD) observation was for Salicylic acid in A2/100 and the lowest RSD (6.2%) was observed in the case of Prednisone at the same setting. Figures 1-4 illustrate these two cases.

Discussion

From Table 1 the highest tablet failure rate of (26%) is observed for Prednisone in the basket apparatus at 50 rpm using non-US data. Similarly, Table 2 shows that the highest run failure rate is 39% using the same apparatus and speed. Interestingly, in both cases (tablet and run failures) there is a difference in the failure rates computed from the US data in comparison to the non-US data at this setting. These observations suggest that Prednisone may be very sensitive to dissolution conditions at this particular setting. A possible explanation for the difference in the failure rates between US and non-US data may be that operators of dissolution tests in some non-US facilities do not always have access to regularly maintained equipment or are perhaps unaware of all the sources of error with the equipment. Although, there seems to be a general consensus about the deaeration methods as being critical, other potential causes for failure should not be overlooked (1). Also issues such as maintenance and rebuilding of the dissolution equipment at regular intervals of time are also critical. Especially

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Table 1: Tablet failure rate of apparatuses tested by USP dissolution calibrators (percentage).

	A1/50 rpm	A2/50 rpm	A1/100 rpm	A2/100 rpm
PREDNISONE				
Global data	11.5	4.1	7.7	6.5
US data	1.8	4.9	6.4	5.9
Non-US data	25.7	2.4	9.8	6
SALICYLIC ACID				
Global data	2.8	3.8	4.1	4.9
US data	1.1	3.3	2.9	3.3
Non-US data	6.4	5.9	5.9	8.7
A1: USP Basket				
A2: USP Paddle				

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Table 2: Run failure rate of USP apparatuses tested by dissolution calibrators (percentage).

	A1/50 rpm	A2/50 rpm	A1/100 rpm	A2/100 rpm
PREDNISONE				
Global data	17.9	10	17.2	12.4
US data	4.3	10.5	14.6	11.5
Non-US data	38.6	9.1	20.4	14.1
SALICYLIC ACID				
Global data	6.9	8.9	7.3	10.7
US data	3.2	6.9	5.6	7.3
Non-US data	14.6	13	10.8	18.4
A1: USP Basket				
A2: USP Paddle				

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Table 3: Percentage RSD for USP dissolution calibrators without failures

		US data		
	A1/50 rpm	A2/50 rpm	A1/100 rpm	A2/100 rpm
Prednisone	0.29 - 35.3	0.19 - 10.0	0.2 - 12.7	0.0 - 23.0
Salicylic acid	0.0 - 15.2	0.0 - 17.9	0.0 - 6.5	0.7 - 13.8
		Non US data		
Prednisone	1.8 - 37.6	1.1 - 7.0	0.0 - 15.4	0.6 - 3.83
Salicylic acid	0.0 - 9.9	1.8 - 18.2	0.0 - 8.5	0.6 - 13.7
A1: USP Basket				
A2: USP Paddle				

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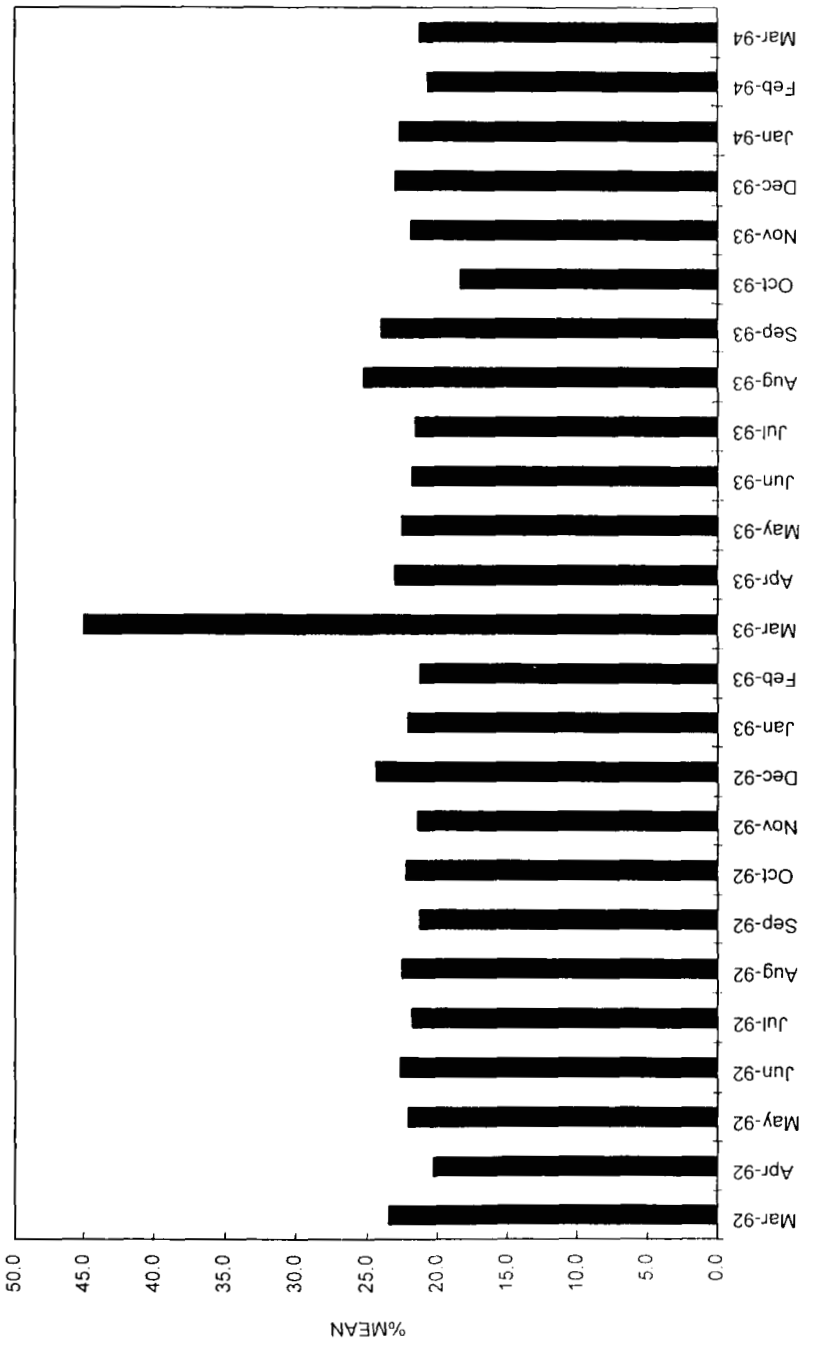

Figure 1. MEAN DISSOLUTION PERCENTAGES FOR SALICYLIC ACID IN A2/100

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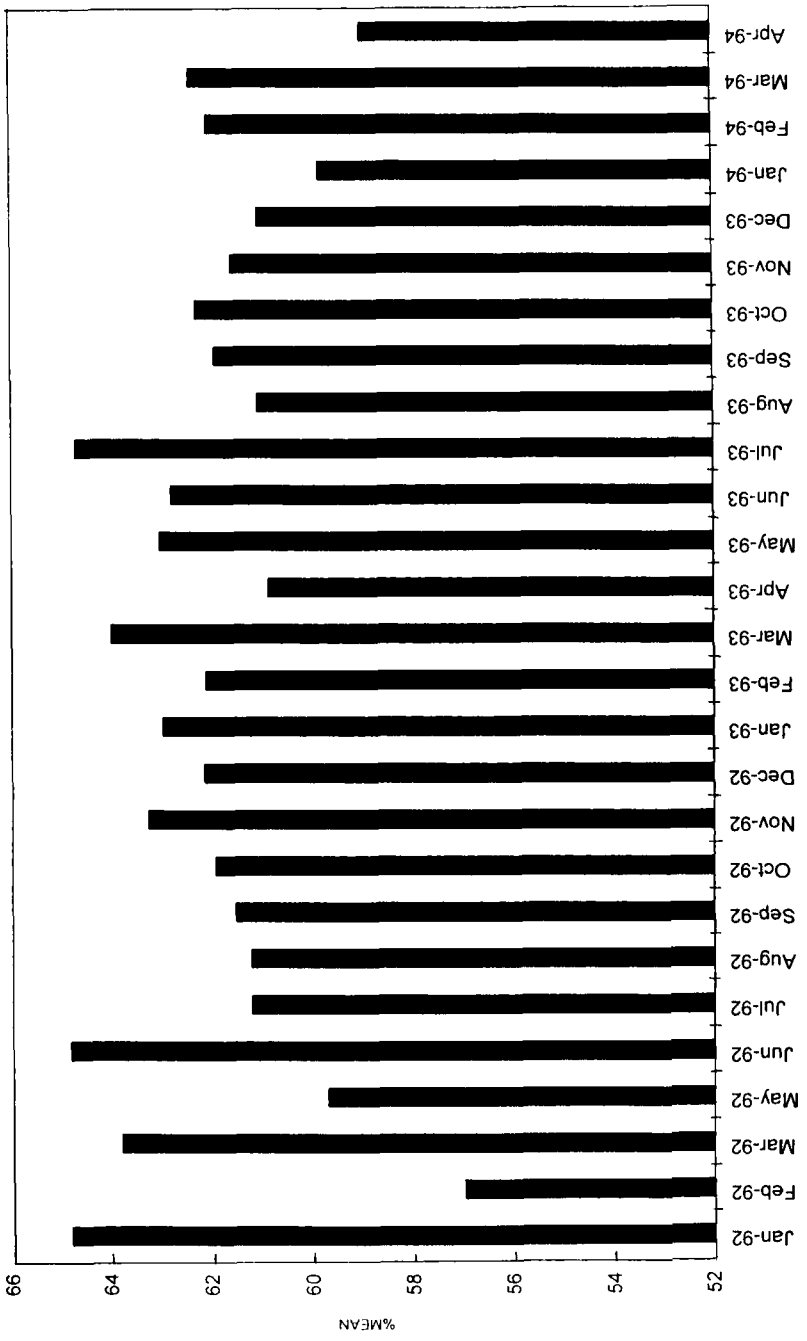

Figure 2. MEAN DISSOLUTION PERCENTAGES FOR PREDNISONE IN A2/100

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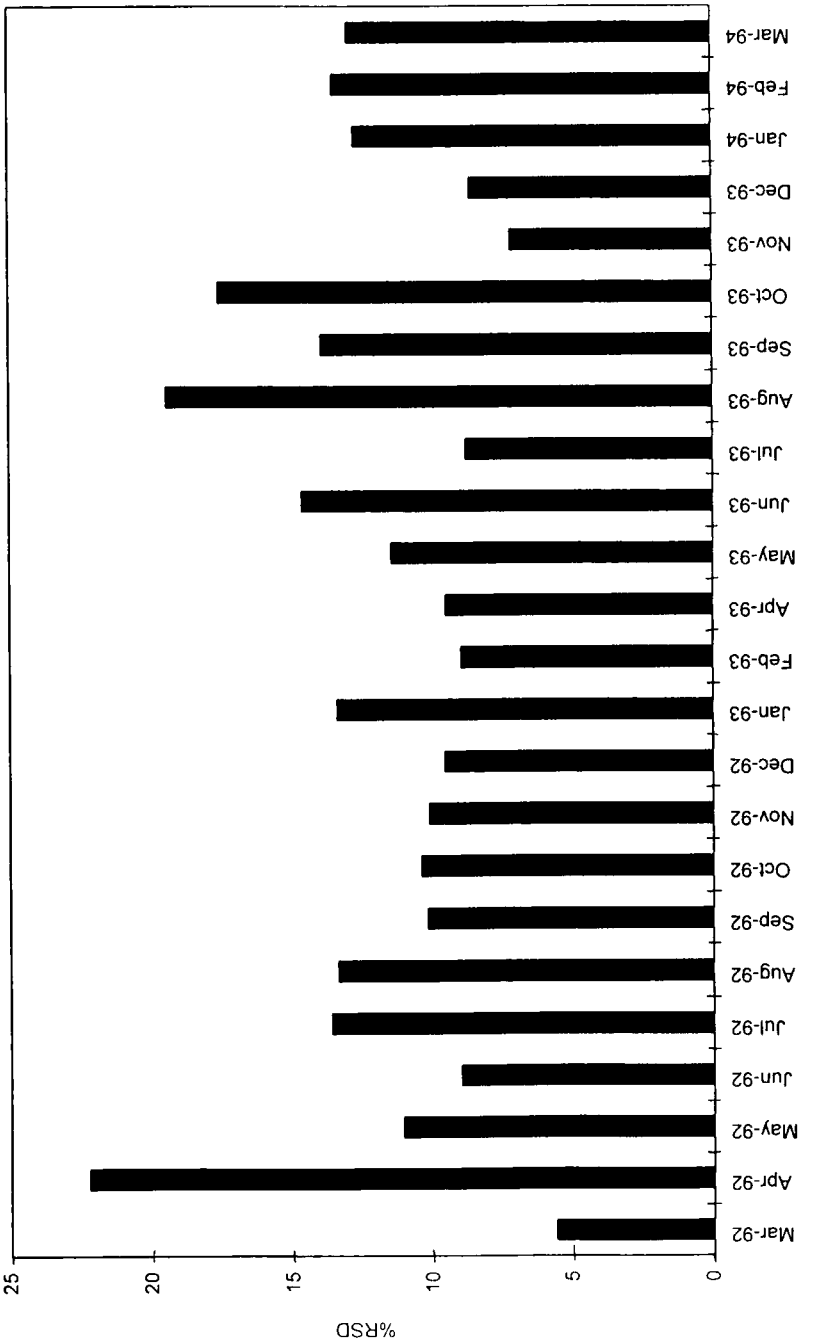

Figure 3. VARIATION IN RSD FOR SALICYLIC ACID IN A2/100

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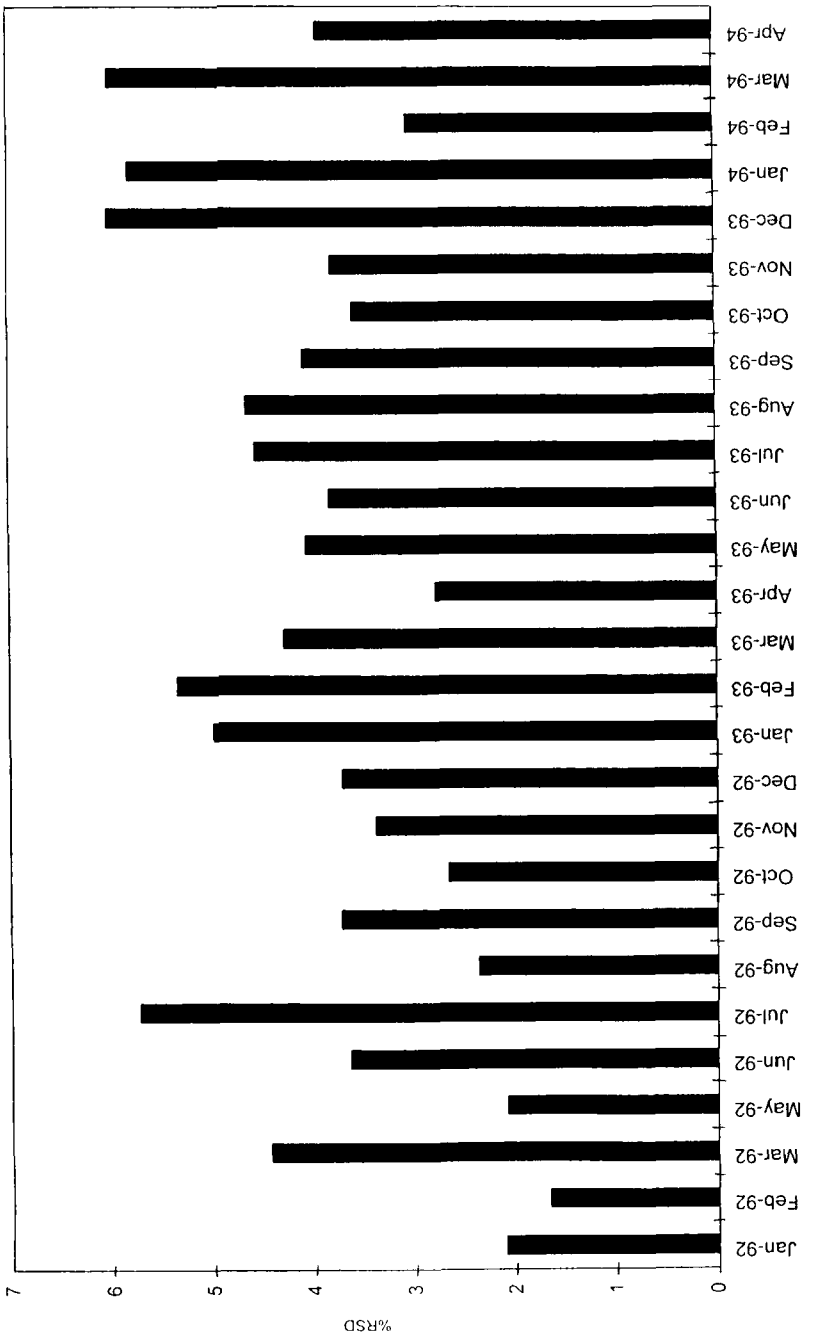

Figure 4. VARIATION IN RSD FOR PREDNISONE IN A2/100

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in countries which are in the early stages of developing robust regulatory structures, organizations such as USP or WHO may be able to provide assistance in training and educating personnel.

A two-tailed matched pair t-test was performed at a p-value of 0.05 to determine statistically significant differences between failure rates from various sources. The failure rates which were found to be significantly different at this level of significance were:

1 Tablet failure rates of Prednisone calibrator tablets between US and non-US data.

2. Run failure rates of Prednisone between US and non-US data.

As reported by Qureshi and McGilveray these differences may be due to variation in the deaeration technique. They reported that heating along with helium sparging or degassing under reduced pressure are the most efficient methods of deaeration (2).

It is USP's earnest objective to constantly improve the performance of its calibrator tablets and bring failure rates to the lowest possible.

From Table 3 it can be inferred that the maximum permissible RSD for acceptable performance of both calibrators is 38%. Analysis of the variation in the mean percentage dissolved against time did not yield an obvious pattern (Figures 1 and 2).

Appendix - I

In this appendix a brief summary of the typical observations and suggestions made by some respondents have been listed. However, these troubleshooting procedures were suggested by the respondents and are not necessarily endorsed by USP.

1. Deaeration procedures critically influence the outcome of the calibration test. A certain respondent reported the decrease of CV and an increase in the percentage mean dissolution when the deaeration technique was changed. The two procedures used were:

   a. Deaeration using stirring hot water (50°C) and vacuum for ten minutes,
   b. Deaeration by filtration using a 0.45 mcm pore size membrane and an ultrasonic bath set at 60°C.

   The latter procedure yielded better results.

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2. A certain respondent reported the use of a silanizing procedure to prevent the tablets from sticking to the baskets. They used an inert food grade silicone spray to prevent adhesion of tablets to the baskets and hence adversely effect the dissolution process. This silicone spray was evaluated for interference in the UV region and found to be inert.

3. The use of a different method to interpret the results was reported by a certain respondent. They adapted the USP <724> drug release interpretation to this situation. They plan to use the "S_2" approach when the identification of instrument failure is not possible.

4. The problem of deposition was observed while calibration was reported. It was found that as the tablets disintegrated in a confined area of the dissolution vessel they formed small deposits alongside the sloping edge of the dissolution vessel. Such deposition was not subject to adequate mixing and hence impacted the dissolution process. In such cases if the vessels were mixed by external means. They yielded satisfactory results.

Acknowledgments

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