AN IMPROVED TEST FOR UNIFORMITY OF WEIGHT OF TABLETS

By K. L. Smith

Standards Department, Boots Pure Drug Co., Ltd., Nottingham

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Introduction

The British Pharmacopœia 1953 includes a test for the uniformity of weight of tablets which requires, that when the tablets in a sample of 20 are weighed singly, not more than 2 deviate from the average weight by a percentage greater than that specified and no tablet deviates by more than double that percentage.

The procedure described in the B.P. may be preferred by those making occasional examinations, but those carrying out the test regularly must often consider that, when there is evidence that the batch is uniform, it should not be necessary to complete the 20 weighings and that, in the absence of a provision to take a further sample, the division between acceptance and rejection is too rigid.

The method of sequential analysis developed by Wald[1] will provide an alternative procedure which meets these criticisms and discriminates between satisfactory and unsatisfactory batches as efficiently as the official test. In this alternative procedure the average weight of 20 tablets is determined and the tablets weighed singly. After each weighing, reference is made to criteria for acceptance and rejection, which can be previously established. If either criterion is reached the examination is halted, if not, the weighings are continued.

Discrimination of the B.P. Test

The values in Table I have been obtained using the standard arithmetical methods which are described in the appendix to this paper. The Table illustrates the probability of accepting, by the official test, batches of tablets containing varying proportions of "defectives." Defectives are defined as tablets having weights which deviate from the average by the amount specified in the B.P. The Table also records the proportions of "double defectives" (tablets deviating by double the specified amount) and of "half defectives" (tablets deviating by half the specified amount) to be expected in these batches.

The Alternative Procedure

It follows from Table I that, if the alternative procedure is to have the discrimination of the official test, it should satisfy the requirements that when a batch of tablets contains 5 per cent. "defectives" there should be 92 chances in 100 of it being accepted and that when a batch contains 25 per cent. "defectives" there should be only 8 chances in 100 of this happening. Using these values in the formulæ given by Wald[1], which are reproduced in the appendix, the numbers of "defectives" critical for acceptance and rejection to be observed in any number of weighings have

been calculated. These are recorded in Table II where the entries involving fractions of tablets are necessarily omitted.

TABLE I

THE PROBABILITY OF ACCEPTING, BY THE OFFICIAL TEST, BATCHES OF TABLETS CONTAINING VARYING PROPORTIONS OF "DEFECTIVES" AND THE PROPORTIONS OF "HALF DEFECTIVES" AND "DOUBLE DEFECTIVES" EXPECTED TO BE PRESENT IN SUCH BATCHES

Proportion of			Probability of acceptance by official test
"Defectives"	"Half defectives"	"Double defectives"	
0·05	0·32	0·0001	0·92
0·10	0·40	0·001	0·67
0·15	0·47	0·004	0·39
0·20	0·52	0·0104	0·19
0·25	0·57	0·0214	0·08
0·30	0·60	0·022	0·03

Table II shows that with the alternative procedure a batch of tablets would be accepted at the eleventh weighing if no "defective" had been found, but that if 2 "defectives" were found in the first 5 weighings, it would be rejected. The batch would not be considered satisfactory if 2 "defectives" were found in 20 weighings, and the weighings would be continued unless 4 "defectives" had been observed in which case the batch would be rejected.

When the occurrence of "defectives" are being observed, no batch, however uniform, could be accepted with less than 11 weighings. High uniformity, however, also shows itself by the lower frequency with which "half defectives" occur. It is seen from Table I that the proportion of "half defectives" present in batches containing 5 per cent. and 25 per cent. "defectives," are 32 per cent. and 57 per cent. respectively. Using these values in the formulæ given by Wald[1] the critical acceptance and rejection numbers for "half defectives" have been calculated and are shown in Table III.

TABLE II

CRITERIA FOR ACCEPTANCE AND REJECTION BY THE IMPROVED PROCEDURE WHEN THE OCCURRENCE OF "DEFECTIVES" IS CONSIDERED

Number of "defectives" observed	Accept if number of tablets weighed is not less than:	Reject if number of tablets weighed is not greater than:
0	11	
1	19	1
2	26	5
3	34	13
4	42	20
5	50	28
6	58	36

The data in Table III shows that by observing the occurrence of "half defectives" not only could a batch of tablets be accepted with as few as 6 weighings, but that the interval between the numbers of weighings at which decisions can be made is smaller than that which obtains when "defectives" are being considered (Table II).

The improved procedure, counting the number of "half defectives," has been adopted for routine assays by a colleague and the information from the examination of 104 consecutive batches of 5 grain aspirin tablets, all of which were acceptable by the official test, is available. It was found that one batch demanded 24 weighings before it could be accepted. The remaining 103 batches were acceptable at or before the 13th weighing, and 96 of them at the 6th or 8th weighings. In the examination of one

other batch of tablets which did not pass the official test in that 3 "defectives" were observed in 20 weighings, it was noted that the first 5 tablets weighed were all "half defectives."

TABLE III

CRITERIA FOR THE ACCEPTANCE AND REJECTION BY THE IMPROVED PROCEDURE WHEN THE OCCURRENCE OF "HALF DEFECTIVES" IS CONSIDERED

Number of "half defectives" observed	Accept if number of tablets weighed is not less than:	Reject if number of tablets weighed is not greater than:
0	6	—
1	8	—
2	10	—
3	13	—
4	15	—
5	17	5
6	19	8
7	22	10
8	24	12
9	26	15
10	28	17
11	31	19
12	33	21
13	35	24
14	37	26
15	40	28

DISCUSSION

The method of sequential analysis has been used to provide an alternative procedure for testing the uniformity of weight of tablets. This alternative procedure discriminates between satisfactory and unsatisfactory batches as efficiently as the official test, using a sample of 20 tablets. It also meets the criticisms made against the official test in that it should not be necessary to complete the 20 weighings when there is evidence of uniformity, and that, in the absence of a provision to take a further sample, the division between acceptance and rejection is severe. The B.P. test has also been criticised by Dunnett and Crisafio[2] who suggest that the use of 20 tablets in the manner described may not be adequate. Methods suggested by them are that the standard deviation of 10 or 20 tablets could be used as a measure of uniformity or that a sample of 50, with provision to halt the examination at 20 tablets, should be taken. If it were permitted to estimate the standard deviation by the range in the tablet weights, the first method would not be laborious, but the criticism of the rigid division between acceptance and rejection would not be met. The objection to the second suggestion lies in the rigidity in the number of weighings demanded. The alternative procedure considered in this paper could be readily applied to give the discrimination of an examination where a sample of 50 was used and 5 "defectives" permitted.

The information obtained by using the alternative procedure in the examination of routine batches of tablets, which were acceptable by the official test, illustrates the saving in the number of weighings to be expected when the occurrence of "half defectives" is noted. Information like this does not prove that the alternative method discriminates as efficiently as the official test, but, on purely theoretical grounds it must, in the long run, do so.

APPENDIX ILLUSTRATING THE ARITHMETICAL METHODS USED TO ESTABLISH VALUES USED IN THE BODY OF THE PAPER

Estimation of the Proportion of Other Specified Percentage Defectives

It is generally accepted that the normal distribution is a satisfactory approximation to the distribution of the weights of tablets in a batch.

Therefore, if x is the value taken from a table of normal distribution[3] which corresponds to the proportion of "defectives," then $2x$ and $0{\cdot}5x$ are the values which correspond respectively to the proportions of "double defectives" and "half defectives" present in the batch.

Discrimination of the B.P. 1953 Test

When the proportion of "defectives" in a batch of tablets is p, the probabilities of obtaining 2, 1 and 0 "defectives" in a sample of 20 are represented by the last three terms of the binomial

$$(p + q)^{20} \text{ where } p + q = 1$$

The sum of these three terms, corrected for the probability that the "defectives" chosen are not "double defectives," will give the probability of acceptance by the official test. If the proportion of "double defectives" present is (p') this sum is equal to

$$190\, p^2 q^{18}\left(1 - \frac{p'}{p}\right)^2 + 20\, pq^{19}\left(1 - \frac{p'}{p}\right) + q^{20}$$

Calculation of the Acceptance and Rejection Numbers

When quality is measured by a proportion possessing a certain characteristic Wald[1] has shown that if the desired probability of rejection of the more acceptable quality (p_0) is α and the desired probability of acceptance of the less acceptable quality (p_1) is β, then the numbers possessing this characteristic to be observed in a sample of size m critical for acceptance and rejection are given by the formulæ

$$\text{Acceptance number} = \frac{m \log \dfrac{1 - p_0}{1 - p_1} + \log \dfrac{\beta}{1 - \alpha}}{\log \dfrac{p_1}{p_0} - \log \dfrac{1 - p_1}{1 - p_0}}$$

$$\text{Rejection number} = \frac{m \log \dfrac{1 - p_0}{1 - p_1} + \log \dfrac{1 - \beta}{\alpha}}{\log \dfrac{p_1}{p_0} - \log \dfrac{1 - p_1}{1 - p_0}}$$

SUMMARY

1. The method of sequential analysis is used to provide an alternative procedure to that described in the B.P. 1953 to test the uniformity of weight of tablets.

2. This alternative procedure allows uniform batches to be accepted with fewer weighings than the official test and removes the rigid division between acceptance and rejection in the borderline cases.

3. When the occurrence of tablets having weights which deviate from the average by half the amount specified in the B.P. is noted, the number of weighings needed in the alternative procedure is greatly reduced.

REFERENCES

1. Wald, *Sequential Analysis*, John Wiley and Sons.
2. Dunnett and Crisafio, *J. Pharm. Pharmacol.*, 1955, **7**, 314.
3. Fisher and Yates, *Statistical Tables for Biological, Agricultural and Medical Research*, Oliver and Boyd.

DISCUSSION

The paper was presented by THE AUTHOR.

DR. F. HARTLEY (London) said that the virtues of the application of the sequential analysis technique had been seen in connection with the pyrogen test. An assumption which must be made in connection with the author's proposal was that there was normal distribution of possible errors and that assumption could not be made when taking an odd sample of 20 tablets. Mr. Smith had made the point—and had been criticised—that a sample of 20 was too small. He submitted that the task of the Pharmacopœia was to enable a clear decision for pass or failure to be reached on the average size of sample which could normally be expected to be taken by prescription or by a public analyst. A good deal hung on the sentence in the second paragraph "when there is evidence that the batch is uniform." In manufacturing additional control was possible and the method was a very helpful statistical tool which simplified the task of routine control of large numbers of batches of tablets. However, decisions had to be taken in borderline cases, and he did not think it advisable for the size of samples to be variable in the official specification.

DR. D. C. GARRATT (Nottingham) said that the method would give the same results with less work and save a great deal of time in large laboratories. Size of the sample was not really an important factor, if instead of taking the defective value, the half defective value was taken.

DR. G. E. FOSTER (Dartford) said he was worried because on modern tablet machines there were as many as twenty punches, and it was necessary to give every punch a chance to supply a tablet to be weighed. One punch might be maladjusted, and if one took only ten tablets and weighed them, tablets from that punch might be missed. Were any batches included in the paper which did not comply with the Pharmacopœial test?

MR. P. S. STROSS (London) said he wondered whether the point made by Dr. Garratt that the method would save time was really true. It was simpler to give the junior analyst tablets to weigh, and get him to write a report from which the senior analyst could decide at a glance whether the tablets complied with the Pharmacopœial requirements or not. If he understood the paper correctly the half defective method was questionable because it assumed normal distribution which would not be the case in a rotary machine with a faulty punch.

MR. E. W. RICHARD (Upminster) suggested that there might be three distinct checks during the life of a batch of tablets. First, at the manufacturing stage there was production control; secondly, when a batch had been completed a test was carried out by the control department and thirdly, there was the sample taken by the public analyst. At the manufacturing stage and possibly at the analytical control stage one might say

that the quantity of material available was unlimited. Many machines turned out more than 20 tablets per revolution and from that point of view alone he disliked the B.P. test. The wider information obtained by weighing a large number of tablets and the time and labour required might be reconciled in the near future, particularly in view of a new electronic device being developed which would enable tablets to be weighed very rapidly. Sequential analysis, although a very useful tool, could possibly then be supplemented at the manufacturing stage by weighing, which would give more information on the product being turned out.

DR. G. BROWNLEE (London) said that unless he had wrongly understood the arithmetic, all that the author was proposing was that better use should be made of the present information. He was not asking readers to assume anything that they did not already assume for the purposes of the B.P. test. The problem became complicated when the second issue was raised, namely, "What are you going to regard as the population that you are examining?" The only way to find out what was the population and how it was distributed was by weighing every tablet. In a process which was going on all day in which one punch might be contributing to skewness quite possibly the population was a hazard over a period of time and tests must be related to time. The B.P. test and the proposed test were both tests to detect abnormal distribution.

DR. R. E. STUCKEY (London) said that the Pharmacopœial test was of little practical value to a public analyst, and in manufacture far more samples than those provided for by the B.P. should be taken for proper control. He was therefore uncertain as to who should use the B.P. test.

MR. A. R. ROGERS (Brighton) agreed that there was a satisfactory approximation to normal weight distribution in good batches but not in unsatisfactory batches. Both the B.P. test and that suggested by the author assumed that the criterion based on normal distribution was adequate.

MR. K. L. SMITH, in reply, said that as to the question who should carry out the B.P. test, the best answer might well be no one. The manufacturer might wish to carry out a more severe one. The public analyst should also be wary of making a decision on a sample in which the pass criterion was not reached. It did not seem unreasonable to have such criteria that firm decisions might be made in the case of good or bad batches, and one of "not proven" in certain intermediate ones. It was of course true that the suggested test did no more and no less than the B.P. test, but it did it efficiently. He had been informed that when tablets made on a single punch machine failed the B.P. test, the distribution of the weights was mostly skew. The fact that the distribution was not always normal did not affect the calculation appropriate to the occurrence of defectives. Normal distribution had only been assumed to estimate the equivalent frequency of the occurrence of half defectives. The effect of the error would, he felt, be small. The suggestion was made that there might be an error in the arithmetic in view of the fact that by the B.P. test three defectives in 20 tablets failed the batch, whereas

in the suggested test four defectives were needed to do that. That was the logical result of a different mathematical approach and was balanced by the fact that one was not permitted to pass a batch when two defectives were observed in 20 tablets. He was not conversant with the vagaries of the odd punch in a multipunch machine but the argument that the taking of a fixed sample of 20 rather than sampling sequentially avoided this was naïve. The evidence of uniformity referred to was the evidence collected during manufacture, and not the evidence collected during the actual test. He had failed to emphasise that decisions with a small number of weighings would be possible only when the batch was uniform.