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Statistical Evaluation of Pharmacopoeia Weight Variation Tests for Tablets using a Ratio Statistic

By SUKALYAN SENGUPTA†

Indian Statistical Institute, Calcutta, India

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SUMMARY

This paper considers the latest pharmacopoeia weight variation tests and calculates the probabilities of passing such tests using the ratio statistic of the form $x_i/\bar{x}$ where the x_i are normally distributed. The probabilities are then compared with those obtained by using the method due to Roberts. Roberts's method leads to underestimates of these probabilities. The results are also used to determine the process conditions to be maintained by a manufacturer to pass the weight variation tests.

Keywords: Pharmacopoeia weight variation tests; Ratio statistic; Probability of passing a test

1. Introduction

Drugs in the form of tablets are one of the main products of the pharmaceutical industries. Active ingredients (i.e. the drug) and filler and binder materials are thoroughly mixed, usually in drum mixers, to prepare a homogeneous granular mass. Measured quantities of these granules are then compressed in high speed rotary die punch compressors to make the tablets. The active ingredient content of a tablet is prescribed by the various pharmacopoeia. However, the quantities of the other materials and thus the weight of the tablet are fixed by the formulation of the particular manufacturer. It is statutory to specify the active ingredient content on the strips or packages of the tablets. However, there is no requirement to indicate the weight of the tablets.

To ensure that the manufacturers control the variation in the weight of the compressed tablets, different pharmacopoeia specify what are termed 'weight variation tests'. These tests are primarily based on a comparison of the weight of the individual tablets (x_i) of a sample of tablets with an upper and lower percentage limit of the observed sample average (mean, $\bar{x}$). As these are regulatory tests, it is important that a manufacturer knows the probabilities of passing such tests, under different process conditions. Roberts (1969) provided a method to evaluate the probabilities of passing the United States Pharmacopoeia (USP) test at that time. This was done by modifying the test to make the comparison with percentage limits of the process average, rather than with those of the sample average. The probabilities of passing this modified test were then obtained assuming x_i to be normally distributed and were

† *Address for correspondence:* SQC & OR Unit, Indian Statistical Institute, 27-B, Camac Street, Calcutta 700016, India

expressed as a function of the coefficient of variation (COV). These probabilities were also taken as the estimates of the probabilities of passing the USP test.

However, it can be seen that such tests can be expressed as limits of the ratio statistic $x_i/\bar{x}$, and then using the results of Hinkley (1969) the probabilities of passing the tests can be calculated easily.

In this paper we consider the latest weight variation tests—the British Pharmacopoeia (BP) test (1980), the Indian Pharmacopoeia (IP) test (1985) and the USP test (1985). The probabilities of passing these tests for different values of the COV have been calculated and compared with those obtained by using Roberts's method. It is seen that Roberts's method underestimates the probabilities in all the situations. Some implications of these tests for the process conditions to be maintained by a manufacturer are also shown.

2. Pharmacopoeia Specification (Weight Variation Tests)

2.1. *British Pharmacopoeia and Indian Pharmacopoeia Tests*

A sample of 20 tablets is taken from any batch. Each tablet is weighed singly and the average for 20 tablets found from the data. No tablet should deviate by more than double the percentage given in Table 1 from the average and not more than two tablets should deviate from the average by the percentage tabulated.

2.2. *United States Pharmacopoeia Test*

A sample of 10 tablets is taken from any batch. Each tablet is weighed individually and the sample average $\bar{x}$ and the relative sample standard deviation $100s/\bar{x}$ are calculated. No tablet should deviate from the average by more than 15% of the average and the relative standard deviation should be less than or equal to 6.

3. Weight Variation Tests as Tests for the Ratio Statistic: $x_i/\bar{x}$

Let x_i have the normal distribution $N(\mu, \sigma^2)$. Symbolically the limits specified by the weight variation tests can be written as $(1-f)\bar{x} \leqslant x_i \leqslant (1+f)\bar{x}$, where $100f$ is the allowable percentage. If we define $w_i = x_i/\bar{x}$, this leads to the new limits $1-f \leqslant w_i \leqslant 1+f$.

Consider two normal variates X_1 and X_2 with $X_1 \sim N(\mu_1, \sigma_1^2)$, $X_2 \sim N(\mu_2, \sigma_2^2)$ and correlation coefficient ρ. Denote $W = X_1/X_2$ and let $F(W)$ be its distribution function. Hinkley (1969) showed that, when μ_2/σ^2 is large, $|F(W) - F^*(W)| \leqslant \text{Prob}\{X_2 \leqslant 0\}$, where

$$F^*(W) = \Phi\left(\frac{\mu_2 W - \mu_1}{\sigma_1 \sigma_2 a(W)}\right),$$

TABLE 1

Average weight of tablets	*Percentage*
80 mg or less	10
Between 80 mg and 250 mg	7.5
250 mg and more	5

Φ being the normal integral and

$$a(W)=\left(\frac{W^2}{\sigma_1^2}+\frac{\rho W}{\sigma_1\sigma_2}+\frac{1}{\sigma_2^2}\right)^{1/2}.$$

In the present case, $\rho=(1/\sqrt{n})$ and $\text{Prob}\{\bar{x}\leqslant 0\}=0$. Hence,

$$F(w_i)=\Phi\left[\frac{\mu\sqrt{n}}{\sigma}\frac{w_i-1}{\sqrt{(w_i^2-2w_i+n)}}\right]=\Phi(z_i), \tag{1}$$

say, where $z_i\sim N(0,1)$. Given f and n, $F(w_i)$ is a function of the COV only. Also since,

$$\frac{Z_i^2\sigma^2}{n\mu^2}=\frac{w_i^2-2w_i+1}{w_i^2-2w_i+n}$$

is quite small, we can write

$$w_i\approx\frac{Z_i\sigma}{\mu}\sqrt{\left(\frac{n-1}{n}\right)}+1.$$

Thus w_i is asymptotically distributed as

$$N\left(1,\frac{n-1}{n}\frac{\sigma^2}{\mu^2}\right). \tag{2}$$

Roberts, by implication of his modification of the test limits, assumed $w_i\sim N(1,\sigma^2/\mu^2)$. Hence Roberts's method would lead to underestimates of the probabilities of passing the tests. For our calculation of the probabilities we shall use equation (1) which gives the true values of $F(w_i)$.

4. Calculation of Probabilities of Passing Tests

4.1. *British Pharmacopoeia and Indian Pharmacopoeia Tests*

Let $P=\text{Prob}\{1-f\leqslant w_i\leqslant 1+f\}$ and $Q=\text{Prob}\{1-2f\leqslant w_i\leqslant 1+2f\}$. Then the probability of passing the BP or the IP test, L (say), is given by

$$L=P^{20}+20P^{19}Q+190P^{18}Q^2 \tag{3}$$

where P and Q are obtained using equation (1).

By using Roberts's method the corresponding probability L_m (say) will be obtained by replacing P and Q in equation (1) with

$$P_m=\Phi\left(\frac{f\mu}{\sigma}\right)-\Phi\left(\frac{-f\mu}{\sigma}\right)$$

and

$$Q_m=\Phi\left(\frac{2f\mu}{\sigma}\right)-\Phi\left(\frac{-2f\mu}{\sigma}\right)-P_m$$

respectively.

We have calculated L and L_m for different values of the COV. Table 2 gives these values of L and L_m. The relative amount of underestimate under Roberts's method, $\Delta=100(L-L_m)/L$, is also given in Table 2.

TABLE 2

Probabilities of passing the weight variation tests (BP or IP)—L (present method) and L_m (Roberts's method), and the relative amount of underestimate under Roberts's method

COV (%)	L	L_m	Δ
Average weight of tablets 80 mg or less			
20	9.49×10^{-7}	6.11×10^{-7}	35.6
10	0.024980	0.018889	24.4
6.67	0.527738	0.464082	12.1
5	0.954820	0.938779	1.7
4	0.998856	0.998096	0.08
3	0.999999	0.999999	0
Average weight of tablets between 80 mg and 250 mg			
20	5.40×10^{-9}	3.37×10^{-9}	37.6
10	6.40×10^{-4}	4.42×10^{-4}	30.9
6.67	0.086382	0.060717	24.5
5	0.529098	0.474720	10.3
4	0.906188	0.879202	3.0
3	0.998858	0.998096	0.08
2.5	0.999999	0.999996	3.0×10^{-6}
Average weight of tablets 250 mg and more			
20	2.48×10^{-12}	1.52×10^{-12}	38.7
10	9.54×10^{-7}	6.11×10^{-7}	36.0
6.67	6.36×10^{-4}	4.34×10^{-4}	31.8
5	0.025053	0.018898	24.4
4	0.190113	0.157218	17.3
3	0.742213	0.694438	6.4
2.5	0.954963	0.938780	1.7
2	0.998860	0.998096	7.6×10^{-4}
1.67	0.999989	0.999937	5.2×10^{-5}
1.5	0.999999	0.999999	0

† $\Delta = 100(L_m - L)/L$ for different values of the COV.

4.2. *United States Pharmacopoeia Test*

The relative standard deviation is the sample COV (c, say). We shall assume c to be normally distributed with $E(c) = \sigma/\mu$ and

$$\sigma^2(c) = \frac{\sigma^2}{n\mu^2}\left(\frac{1}{2} + \frac{\sigma^2}{\mu^2}\right).$$

The accuracy of this approximation is very good especially for small c and moderately large n (Inglewicz and Myers, 1970). Let $P = \text{Prob}\{1 - f \leqslant w_i \leqslant 1 + f\}$, $P_2 = \text{Prob}\{c \leqslant 0.06\}$ and $P_1 = P^{10}$. It can be easily verified that for a normal variate the correlation coefficient between that variate and its COV is zero. Using this fact and result (2), we can consider the probability of passing the USP test as $L = P_1 P_2$. L_m is obtained similarly by using $P_{1m} = P_m^{10}$ in place of P_1. Table 3 gives the values of L, L_m and the relative amount of underestimate under Roberts's method, $\Delta = 100(L - L_m)/L$, for different values of the COV.

5. Comments

Whereas Roberts's method gives underestimates of the probabilities of passing the weight variation tests, the present method gives exact values of the probabilities for

TABLE 3

Probabilities of passing the USP weight variation test—L (present method) and L_m (Roberts's method) and the relative amount of underestimate under Roberts's method†

COV (%)	L	L_m	Δ
20	4.00×10^{-8}	2.62×10^{-8}	34.5
10	0.001695	0.001360	17.6
6.67	0.219981	0.205598	6.5
5	0.882329	0.872569	0.9
4	0.998404	0.997438	0.1
3	0.999999	0.999817	0.02

† $\Delta = 100(L - L_m)/L$ for different values of the COV.

tests other than the USP test. For the USP test also, our method gives better estimates since the values of P_1 used are the true values.

Under the BP or the IP tests, to pass the test with 0.999 999 probability, i.e. almost always, the manufacturing process should be so controlled as to have the COVs as follows:

(a) for heavy weight tablets (average weight greater than 250 mg), COV $\leqslant 1.5\%$,
(b) for medium weight tablets (average weight between 80 mg and 250 mg), COV $\leqslant 2.5\%$,
(c) for light weight tablets (average weight 80 mg or less), COV $\leqslant 3.0\%$.

In industrial situations, 6σ is usually considered as the process capability. This is because $\pm 3\sigma$ limits contain 99.73% of the area under the normal curve. Thus if a manufacturer makes tablets of three different average weights, e.g. 300 mg, 150 mg and 75 mg, to pass the tests the process capabilities required would be 27.0 mg, 22.5 mg and 13.5 mg respectively.

Under the USP, to pass the test with the same probability the COV must be less than or equal to 3.0%. This implies that for the same set of the three average weights given in (a), (b) and (c) the process capabilities required would be 54 mg, 27 mg and 13.5 mg respectively. This permits a manufacturer who follows the USP test a much more relaxed process for the heavy weight tablets.

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