The use of confidence intervals in biopharmaceutics

ERYL SHIRLEY, *Huntingdon Research Centre, Huntingdon, U.K.*

As has been pointed out by Westlake (1972, 1973) significance testing alone is not sufficient in assessing the bioavailability or effectiveness of new drug formulations. A new formulation may not be significantly different from a standard formulation in, say, bioavailability but because of the wide variability in the observations made or insufficient numbers of subjects in the trial, the confidence limits for the difference between the formulations may be broader than is acceptable. For instance, there might be a non-negligible probability that the two formulations differed by as much as 50% of the standard. On the other hand the new formulation might be significantly different from the standard but the 95% confidence limits only encompass a difference of 5% in which case the new formulation might still be acceptable.

Confidence limits for the difference between the standard and test formulation values for some parameter of interest e.g. extent of bioavailability are derived under the assumption that

$$Z = \frac{\bar{x}_S - \bar{x}_T - \mu_S + \mu_T}{\text{s.e.d.}}$$

is distributed as the *t*-distribution, where μ_T and μ_S are the population means of the test and standard formulations respectively, $\bar{x}_T$ and $\bar{x}_S$ are the corresponding sample means obtained in the trial, and s.e.d. is the standard error of the difference between the sample means, as obtained from the trial data.

The s.e.d. is calculated as $\sqrt{S^2\left(\frac{1}{n_1}+\frac{1}{n_2}\right)}$

Where S^2 is the pooled within group variance or residual variance and n_1 and n_2 are the sample sizes of the two groups of observations being compared. By population mean is meant the mean that would be found if an infinite size sample could be obtained.

The *t*-distribution is a symmetric distribution and it is therefore natural when seeking 95% confidence limits to choose k and $-k$ such that $\int_{-k}^{k} t(z)\,dz = 0{\cdot}95$ as illustrated in Fig. 1.

This leads to the form of 95% confidence interval

$$-k \leqslant \frac{\bar{x}_S - \bar{x}_T - \mu_S + \mu_T}{\text{s.e.d.}} \leqslant k$$

i.e. $\bar{x}_T - \bar{x}_S - k \times \text{s.e.d.} \leqslant \mu_T - \mu_S \leqslant \bar{x}_T - \bar{x}_S + k \times \text{s.e.d.}$

or $\mu_S + a \leqslant \mu_T \leqslant \mu_S + b$

where $a \neq -b$

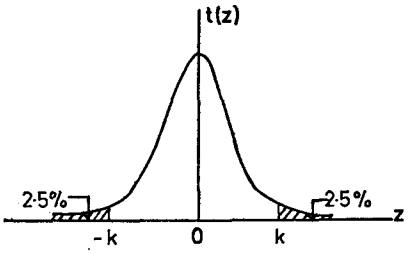

FIG. 1. 95% confidence interval which is symmetric about the underlying '*t*'-distribution.

Westlake (1972, 1973) suggested that it is sometimes more convenient to have the confidence interval in the form $\mu_S - c \leqslant \mu_T \leqslant \mu_S + c$ from which can be derived statements such as 'The new formulation is within ±20% of the standard formulation'. He derived formulae for a confidence interval of the form

$$k_1 \leqslant \frac{\bar{x}_S - \bar{x}_T - \mu_S + \mu_T}{\text{s.e.d.}} \leqslant k_2$$

where $-(\bar{x}_S - \bar{x}_T) + k_1 \times \text{s.e.d.} = -(-(\bar{x}_S - \bar{x}_T) + k_2 \times \text{s.e.d.})$

i.e. $k_1 + k_2 = 2\frac{(\bar{x}_S - \bar{x}_T)}{\text{s.e.d.}}$

and $\int_{k_1}^{k_2} t(z)\,dz = 0{\cdot}95$

Such confidence intervals are consequently asymmetric about the underlying *t*-distribution. If $\bar{x}_T - \bar{x}_S > 0$ they are of the form illustrated in Fig. 2, $k_1 + k_2$ being negative, and if $\bar{x}_T - \bar{x}_S < 0$ they are of the form illustrated in Fig. 3, $k_1 + k_2$ being positive. Such confidence intervals obey the basic condition of a 95% confidence interval, namely that 95% of the distribution lies in this interval. However, it should be noted that these confidence intervals will contain many values such that the probability of such large differences between test and standard means (negative differences if $\bar{x}_T - \bar{x}_S > 0$ and positive differences if $\bar{x}_T - \bar{x}_S < 0$) is less than 0·025 and, more important, they will exclude some values such that the probability of such large differences between means is greater than 0·025 (positive differences if $\bar{x}_T - \bar{x}_S > 0$ and negative differences if $\bar{x}_T - \bar{x}_S < 0$).

On examining Figs 1, 2 and 3 it can be seen that when a positive difference is found between test and standard formulations in the trial (i.e. $\bar{x}_T - \bar{x}_S > 0$) the confid-

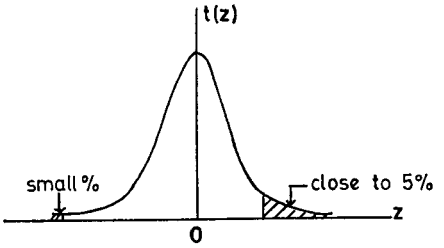

FIG. 2. 95% confidence interval which is shifted away from positive differences.

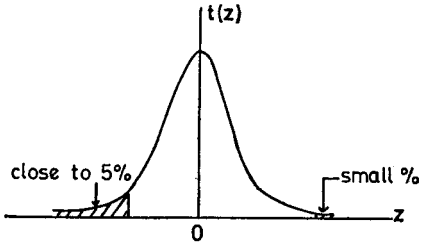

FIG. 3. 95% confidence interval which is shifted away from negative differences.

ence interval is shifted downwards away from this difference when compared with the usual confidence interval symmetric about the *t*-distribution, and when a negative difference is found in the trial, the confidence interval is shifted upwards.This is less than satisfactory because one is shifting the confidence interval away from the direction in which the sample difference has been found.

If confidence intervals of the form $\mu_S - c \leqslant \mu_T \leqslant \mu_S + c$ are required a more cautious approach would be to take the larger of the two values a and b (ignoring signs), m say, obtaining the interval $\mu_S - m \leqslant \mu_T \leqslant \mu_S + m$. Such an interval would contain values beyond the 2·5 percentiles of the *t*-distribution but would not exclude values within the 2·5 percentiles. If a difference in one direction is of more concern than a difference in the other then one should certainly ensure that no points within the 2·5 percentile in this direction are excluded from the confidence interval. Confidence intervals which are symmetric about the mean of the standard formulation rather than the underlying *t*-distribution can be misleading as the following example shows.

Example

Suppose $\bar{x}_S = 11{\cdot}0$ and $\bar{x}_T = 9{\cdot}75$, that s.e.d. = 0·50 and that there are ten degrees of freedom associated with the standard error. If μ_S and μ_T are the true means, then $Z = \dfrac{1{\cdot}25 - \mu_S + \mu_T}{0{\cdot}50}$ is distributed as Student's *t* with ten degrees of freedom. Taking 95% confidence intervals symmetric about the mean, 0, of the *t*-distribution we find $\int_{-2{\cdot}228}^{2{\cdot}228} t(z)\,dz = 0{\cdot}95$

i.e. $$-2{\cdot}228 \leqslant \frac{1{\cdot}25 - \mu_S + \mu_T}{0{\cdot}50} \leqslant 2{\cdot}228$$

or $$-2{\cdot}36 \leqslant \mu_T - \mu_S \leqslant -0{\cdot}14$$

The fact that the two formulations are found to be significantly different when a *t*-test is performed is reflected in the fact that this interval does not cover 0. As a percentage of the standard mean value, 11, this interval becomes −21·5% to −1·3%.

Thus if these were the results of a bioavailability study the test formulation could be said to have reduced bioavailability by up to 21·5%.

k_1 and k_2 are obtained from the conditions

$$k_1 + k_2 = \frac{2 \times 1{\cdot}25}{0{\cdot}50} = 5{\cdot}00$$

and that $\int_{k_1}^{k_2} t(z)\,dz = 0{\cdot}95$.

The values $k_2 = 6{\cdot}812$ and $k_1 = -1{\cdot}812$ obey these conditions accurately enough for practical purposes. These values give a confidence interval for $\mu_T - \mu_S$ of $-2{\cdot}16 \leqslant \mu_T - \mu_S \leqslant 2{\cdot}16$ or, in terms of percentage of the standard formulation mean −19·5% to 19·6%. This confidence interval does not reflect the fact that the probability of a positive difference is small and if the upper limit to acceptability was a difference of 20% between formulations, the formulation would be accepted whereas using the usual type of confidence interval it would be rejected.

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REFERENCES

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