Appendix One

How is Bioequivalence Established?

Bioequivalence is established by undertaking a single or in certain circumstances a number of bioequivalence studies.

Most bioequivalence studies employ a randomised crossover design in healthy volunteers, in which each individual acts as his/her own control. Clearance, volume of distribution, and physiological variables that might affect absorption (e.g. gastric emptying, motility, pH), distribution and elimination will normally have lower within-patient than between-patient variability. Therefore, a crossover design will usually have more statistical power for a given number of subjects than a parallel-group design.

The test (generic) and reference (innovator) products should be administered with a standard quantity of water under fasting conditions or following a standard meal.

So that each subject returns to a 'baseline' state prior to each treatment period, a 'washout' period of no treatment should be employed between each treatment period. The washout period should be at least 5 half lives of the substances to be measured and the absence of carryover of plasma concentrations into the second period should be confirmed by pre-dose plasma assay. If significant carryover is present in the data, the trial results will be considered void.

Sampling times should be appropriate to describe the absorption, distribution, and elimination phases of the drug. Sampling frequency around T_{max} should be sufficient to provide an accurate estimation of C_{max}. Sampling duration should be sufficient to provide an accurate estimation of AUC extrapolated to infinity (measured AUC0-t should be at least 80% of extrapolated AUC0-∞). At least three to four samples can be obtained during the terminal log-linear phase of the elimination period in order to calculate terminal elimination rate constant accurately.

Usually drug or metabolites are measured in serum or plasma. Where plasma measurement is not possible total urine collection may be more appropriate for analysis.

The number of subjects required for a bioequivalence study is determined statistically and is typically about 20, although smaller numbers can be used if sufficient statistical power has been determined.

Plasma concentration curves for the test and the reference product are derived from the data obtained in the study (see Figure 1, page 5). As it is very difficult to test whether two curves are sufficiently similar to each other the internationally accepted indices of area under the curve (AUC), peak and timing of the peak drug concentration (Cmax) are used to characterise the curves. If differences are apparent between either the values for the Cmax of the two products or those for the AUC then the two curves will have different shapes.

The data from each individual patient is used to calculate the mean, standard deviation and confidence intervals of the pharmacokinetic variables (Cmax and AUC).

Statistically the assessment of bioequivalence is based upon 90% confidence intervals for the ratio of the population geometric means (test/reference) for the variables under consideration. This method is equivalent to two one-sided tests with the null hypothesis of bioinequivalence at the 5% significance level.