



## Reviews and Case Studies

### EquivTest™ - A CRO Perspective

#### EquivTest™ reviewed by Independent Data Management - A Leading Irish CRO

Independent Data Management Ltd., is a Contract Research Organisation based in Cork, Ireland. We specialize in clinical trial consultancy and management and pharmacokinetic and biostatistical analysis. Because we analyze data from a large number of bioequivalence studies for sponsors submitting applications to various national regulatory authorities, EquivTest has proved a very useful package.

The first striking feature of EquivTest is its data management capability. The data we receive from crossover trials can be recorded as either multiple variables per subject or multiple records per subject. Rather than having to dictate to our clients which style we require, EquivTest can accommodate both styles. This, together with the broad range of packages supported in the import facility, makes data importation quick and effortless.

Though most pharmacokinetic parameters in a bioequivalence study are analysed using parametric techniques, some need to be analysed using non-parametric techniques. Previously this entailed exporting the relevant data from one statistical package via a text file to a specialized non-parametric package. EquivTest gives us the option of including a non-parametric analysis in the output report. This feature is very useful and especially so when the assumptions underlying parametric analyses are in doubt.

For most bioequivalence studies, the equivalence bounds are 80% to 125% of the reference mean on the logarithmic scale. When the therapeutic window for a drug under investigation is narrow, these bounds need to be narrower. Likewise when the therapeutic window is broader, the bounds can be broader. EquivTest allows the user to specify the equivalence bounds relevant to the particular study protocol.

Another excellent feature is the output report. This report can be tailored to include all or any of the descriptive statistics, Analysis of variance results, Shuirmann's one-sided t-test(s) and non-parametric statistics. The output is clear and concise. Different sections are clearly defined. The report is written in language easily understood by the non-statistician and it can easily be integrated into a final study report.

Since the release of EquivTest, the analysis of bioequivalence studies can be quick, easy and programming-free. All statistical methods required by the FDA and CPMP guidelines are available in one easy-to-use package.

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## **Of Drafts and Gales** **Stephen Senn**

*Just because something can be done doesn't mean that it should be done. Sometimes the game is not worth the candle.*

Statisticians have been arguing about bioequivalence for years. About what the limits for relative bioavailability should be : 80% to 120%, or 80% to 125% or even 83% to 120 %. About how the confidence intervals should be calculated: centred about the point estimate or centred about the point of exact equivalence. About what the level of confidence should be: 95% or 90%. About whether the data should be log-transformed or whether they should use Fieller's theorem and so forth. Now they have found a new bone of contention. The FDA has suggested that average bioequivalence, a comparison of formulations in terms of location alone, will no longer be adequate. Prescribability, which concerns dispersion as well as location, will have to be demonstrated and, in the case of bioequivalence involving reference to marketed products, switchability will have to be demonstrated too.

So what is switchability? For a generic G to be switchable with a brand name B requires not only that a naive patient, one who is currently untreated, would be indifferent as to which (s)he would take but that the same would apply to a patient currently being treated with B: that this patient should notice no difference in being switched. This requires that not only should the means and variances of the two formulations be the same but that there should be no formulation by treatment interaction. As all statisticians know, but many physicians apparently do not, to study interactions requires replication, so that if switchability must be demonstrated and the possibility of subject by formulation interaction needs to be examined, then formulations have to be replicated within subjects. This means that the FDA is currently proposing that the two period AB/BA cross-over design be replaced by four period cross-over designs, using, for example, the sequences ABAB/BABA, and that as a consequence bioavailability trials will become more complicated.

As even some statisticians have forgotten, however, the size of interactions is affected by the size of the main effect. The main effects in this case are formulation and subject. The formulations, of course, are the fixed object of the study but the healthy volunteers usually recruited as subjects are not. They can only be an adequate substitute for patients to the extent that the difference between formulations is constant irrespective of what sort of subject is chosen: who you are does not affect what you show. But this, of course, is precisely what any investigation of switchability cannot assume. This means (whether or not the FDA has realised this) that to investigate this problem seriously, patients and not healthy volunteers will have to be studied. This will make bioequivalence studies even harder to run, since patients will have to be sampled frequently on four separate occasions.

So switchability will come at a cost. It seems appropriate to ask after the potential benefits. Well, of course, the need to demonstrate switchability will protect brand names so that a benefit will be seen in profits for the companies that own them. It will also drive up the price of statistical advice and it will provide more work for regulators. So three interest groups will benefit. Generic companies and reimbursors, on the other hand, will not be so happy. But what about patients? Will they not be protected from risks that they formally ran?

To the extent that formulations that are equivalent in the average sense are not switchable, they will be. (There is no evidence beyond the anecdote, however, that lack of switchability has ever caused any groups of patients serious problems.) But it should not be forgotten that the risks run by a patient who switches are less than those run by a patient who takes a brand name or a generic treatment for the first time. However, this latter risk must be acceptable or the brand name could not have been registered in the first place. It would thus be illogical and inconsistent to prevent registration on grounds of lack of switchability alone. There is another illogicality.



There is nothing (except the cost) to stop a sponsor registering a formulation through a free-standing dossier. Having done so, patients may be switched. But bioequivalence is meant to be a substitute for having to produce such a free-standing dossier. Therefore for bioequivalence as an alternative route of registration, switchability should not be an issue. Only if bioequivalence were an end itself would the issue arise.

And there is yet a further curiosity. According to the FDA's draft guideline, abbreviated antibiotic drug applications (AADAs) will also have to cover switchability. But antibiotics are frequently given in a single course of treatment so that there are very few opportunities for switching patients anyway. Of course, physicians may switch their prescribing habits but that is another matter altogether,

So this is definitely one for burning. Life's too short: even the life of a regulator. There are more important matters to consider. When it come to bioequivalence, drafts aren't nearly strong enough. It is gales of common-sense that we need.



## Statistical Significance and Clinical Relevance: A Contradiction? Prof. Dr. Dieter Hauschke

### 1. INTRODUCTION

The most convincing way to establish efficacy of a new investigational treatment is to demonstrate clinically significant superiority to a concurrent placebo group. In the past, data from such trials have been usually analysed by testing the traditional null hypothesis of no difference in the effect between the treatments. However, the most important drawback of this classical approach is the fact that only the presence or absence of an effect is considered ignoring the issue of effect size. Hence, a statistically significant result gives only the information that the treatment difference is not zero but not providing an answer to the clinical relevance. Therefore, this practice has been criticised and the use of confidence intervals is advocated by regulatory guidelines (1). However, without the concept of the clinically significant (relevant) difference, the two methods are only technically different. Thus, the adequate test problem should be formulated by incorporating the clinically significant difference, resulting in an equivalence of statistical and clinical significance.

### 2. TESTING SHIFTED NULLHYPOTHESES

A two-sample situation is considered and let the clinical endpoint be denoted as  $X_1$  for the test treatment and by  $X_0$  for the control group. Suppose that these random variables are mutually independent and have a continuous distribution function from a location family, that is  $X_{ij} \sim F(x - \mu_j)$ ,  $j = 1, \dots, n_j$ ,  $i = 0, 1$ . Without loss of generality, it is assumed that it is a priori known that if there is a favourable response to the treatment it will increase in magnitude, and hence, indicating the appropriateness of an one-sided alternative. The traditional test problem is formulated as follows:

$$H_0 : \mu_1 - \mu_0 \leq 0 \text{ versus } H_1 : \mu_1 - \mu_0 > 0 .$$

Rejection of the null hypothesis by a statistical test at level  $\alpha$  (e.g. Student's t-test or Wilcoxon test) could provide evidence for the conclusion that there is a clinical relevant effect of the treatment. However, large sample sizes and little variation may lead to the problem that a clinically unimportant difference will be declared statistically significant. Suppose that a difference  $\mu_1 - \mu_0 = \delta > 0$  is considered the maximum clinically irrelevant difference. If the true expected difference is less or equal than this threshold value, then a statistically significant result for the above test problem may be of little interest because the difference is not clinically significant (2, 3). Consequently, the adequate test problem should be formulated as follows:

$$H_0^\delta : \mu_1 - \mu_0 \leq \delta \text{ versus } H_1^\delta : \mu_1 - \mu_0 > \delta ,$$

where  $\delta, \delta > 0$ , denotes the maximum clinically irrelevant difference and hence, this definition implies that only differences greater than  $\delta$  are regarded as clinically important. It should be noted that current statistical methodology can be applied for analysing this shifted null hypothesis (4).

### 3. CONCLUSION

Testing a non-zero null hypothesis instead of one of no treatment difference removes at a stroke some logical problems. For example, one problem of testing the classical null hypothesis is that



even for the most minute true difference between two treatments the p-value will indicate statistical significance if the sample size is big enough. When data are analysed by testing shifted hypotheses larger sample size will increase the probability of obtaining a conclusive result, that is a statistically and clinically relevant significance.

### References:

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### About the Author

Dieter Hauschke has extensive experience in theoretical and practical aspects of equivalence trials and its application to pharmaceutical drug development including bioequivalence, therapeutic equivalence and safety assessment. He has worked at ALTANA Pharma, formerly Byk Gulden Pharmaceutical, since 1986. Dieter Hauschke is author or co-author of over 70 research articles and book chapters He is author of the textbook "Bioequivalence in Drug Development: Methods and Applications, Wiley, Statistics in Practice" (with V. Steinijans and I. Pigeot). In 1999, Dieter received the *venia legendi* ("Habilitation") and in 2004 he was appointed to Professor of biometry at the University of Dortmund.