ANNEX VIII

GUIDANCE FOR SECTION 11.4.2 - STATISTICAL/ANALYTICAL ISSUES AND APPENDIX 16.1.9

A. STATISTICAL CONSIDERATIONS

Details of the statistical analysis performed on each primary efficacy variable should be presented in an appendix. Details reported should include at least the following information:

a) The statistical model underlying the analysis. This should be presented precisely and completely, using references if necessary.

b) A statement of the clinical claim tested in precise statistical terms, e.g., in terms of null and alternative hypotheses.

c) The statistical methods applied to estimate effects, construct confidence intervals, etc. Literature references should be included where appropriate.

d) The assumptions underlying the statistical methods. It should be shown, insofar as statistically reasonable, that the data satisfy crucial assumptions, especially when necessary to confirm the validity of an inference. When extensive statistical analyses have been performed by the applicant, it is essential to consider the extent to which the analyses were planned prior to the availability of data and, if they were not, how bias was avoided in choosing the particular analysis used as a basis for conclusions. This is particularly important in the case of any subgroup analyses, because if such analyses are not preplanned they will ordinarily not provide an adequate basis for definitive conclusions.

   (i) In the event data transformation was performed, a rationale for the choice of data transformation along with interpretation of the estimates of treatment effects based on transformed data should be provided.

   (ii) A discussion of the appropriateness of the choice of statistical procedure and the validity of statistical conclusions will guide the regulatory authority's statistical reviewer in determining whether reanalysis of data is needed.

e) The test statistic, the sampling distribution of the test statistic under the null hypothesis, the value of the test statistic, significance level (i.e. p-value), and intermediate summary data, in a format that enables the regulatory authority's statistical reviewer to verify the results of the analysis quickly and easily. The p-values should be designated as one- or two-tailed. The rationale for using a one-tailed test should be provided.

   For example, the documentation of a two-sample t-test should consist of the value of the t-statistic, the associated degrees of freedom, the p-value, the two sample sizes, mean and variance for each of the samples, and the pooled estimate of

variance. The documentation of multi-center studies analysed by analysis of variance techniques should include, at a minimum, an analysis of variance table with terms for centers, treatments, their interaction, error, and total. For crossover designs, the documentation should include information regarding sequences, patients within sequences, baselines at the start of each period, washouts and length of washouts, dropouts during each period, treatments, periods, treatment by period interaction error, and total. For each source of variation, aside from the total, the table should contain the degrees of freedom, the sum of squares, the mean square, the appropriate F-test, the p-value, and the expected mean square.

Intermediate summary data should display the demographic data and response data, averaged or otherwise summarised, for each center-by-treatment combination (or other design characteristic such as sequence) at each observation time.

B. FORMAT AND SPECIFICATIONS FOR SUBMISSION OF DATA REQUESTED BY REGULATORY AUTHORITY'S STATISTICAL REVIEWERS

In the report of each controlled clinical study, there should be data listings (tabulations) of patient data utilised by the sponsor for statistical analyses and tables supporting conclusions and major findings. These data listings are necessary for the regulatory authority's statistical review, and the sponsor may be asked to supply these patient data listings in a computer-readable form.