

Introduction

The case considered here is when a pharmacokinetic (PK) study is performed in a special population (i.e. a specific ethnic group, a high risk population such as renally or hepatically impaired subjects, ...) without a control group. The purpose is to show average bioequivalence of the PK in this specific population to the PK in the reference population using all previous knowledge summarized with a population PK model. Such an approach is an alternative to the classical analyses based on parallel group trials.

Objective

To propose statistical methods to show the absence of difference in PK (average bioequivalence) between the sample obtained from a special population and the reference population PK model. These statistical methods can be applied either to standard PK parameters (AUC and C_{max}) or to the whole PK profile. The latter approach is sometimes more relevant.

Methods

The following methods were investigated, using simulations with the reference model:

- a method based on non-compartmental analysis (NCA) to study standard PK parameters (for rich sampling studies), and
- a method based on an extension of visual predictive checks (VPC) for mean concentrations to study the whole PK profile (in rich or sparser sampling studies).

Notation:

M^R = the reference population PK model already developed

T = the investigated trial in the special population.

For both methods, PK parameters (i) or PK profile (ii):

The first step was to define the reference means under M^R for the parameters or for the concentrations, using the population model.

This was done through simulation of K individuals using M^R with the design of T, with K being large enough (here, K=1000).

For the equivalence limits, the usual values, 0.80 and 1.25, were used for both AUC and C_{max} , and by homogeneity, similar limits were used for the whole PK profile.

For the method based on PK parameters (i):

AUC and C_{max} were computed by NCA for each subject of T and each of the K simulated individuals using the sampling times of T.

Reference mean μ^R was computed as the exponential of the sample mean of log parameters from the K simulated individuals.

For T, sample mean and standard deviation of individual log(AUC) and log(C_{max}) were computed. The 90% confidence intervals (CI) for the geometric mean parameters were then derived taking the exponent of the limits of the 90% CI on the log parameters.

For each PK parameter, average bioequivalence between T and M^R was shown if the 90% CI for the geometric mean parameters on T was included in $[\mu^R \times 0.8; \mu^R \times 1.25]$.

For the method based on the PK profile (ii):

The reference mean concentration was computed, at each scheduled time, as the exponential of the sample mean of log concentrations from the K simulated individuals.

For T, sample mean and standard deviation of individual log concentrations were computed at each scheduled time, and the 90% CI for the geometric mean concentration was derived.

In case of average bioequivalence between T and M^R , it was expected that the 90% CI of the observed geometric means on T lied within the reference geometric mean times 0.8 and times 1.25. This can be illustrated on a graph of concentrations versus time.

Conclusion

An approach was proposed here to assess average bioequivalence using simulation of the PK profile from the reference model.

PK profile is more demanding than approach by AUC and C_{max} as illustrated here. Furthermore this approach based on the PK profile can be used in more sparse design, whereas the approach based on PK parameters, as presented here using NCA, is limited to rich sampling studies. The approach on parameters could be extended to more sparse sampling situation but necessitates to model the data of T.

Finally, the use of a reference PK model is an interesting approach where there is no control group in special population.

Illustration

To illustrate those methods, a two-compartment population PK model that had been developed for a compound in development, SX [1], was used as M^R .

Two datasets were simulated ($N_{\text{subjects}} = 100$ and $n_{\text{observations/subject}} = 16$): the first one (T_{true}) was simulated with the parameters values estimated in M^R and the other one (T_{false}) was simulated using the same model but with a bioavailability parameter multiplied by 1.5. To perform these methods on PK parameters and on PK profile, K=1000 individuals were simulated.

T_{true}

T_{false}

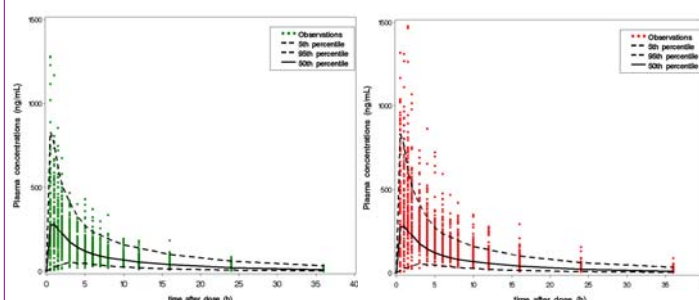


Figure 1: Green and red: observed concentrations in T versus time

Black: 5th, 50th and 95th percentiles simulated by M^R

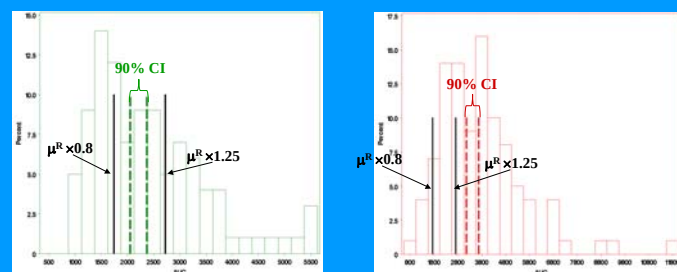


Figure 2: Green and red: histogram of individual AUC on T obtained by NCA and 90% CI of the geometric mean of AUC on T

Black: prediction limits ($\mu^R \times 0.8$) and ($\mu^R \times 1.25$) with M^R

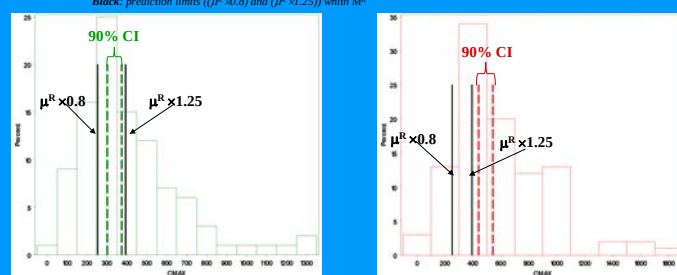


Figure 3: Green and red: histogram of individual Cmax on T obtained by NCA and 90% CI of the geometric mean of Cmax on T

Black: prediction limits ($\mu^R \times 0.8$) and ($\mu^R \times 1.25$) with M^R

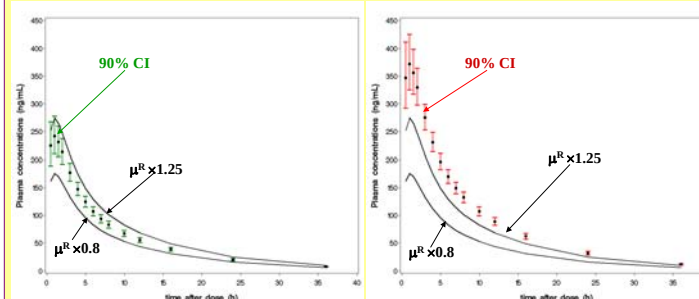


Figure 4: Green and red: mean plasma concentrations of T and 90% CI of the observed geometric means on T

Black: prediction limits ($\mu^R \times 0.8$) and ($\mu^R \times 1.25$) simulated by M^R

As expected for Figures 2 and 3, the 90% CI of the mean of AUC and C_{max} lied within the equivalence limit computed with M^R with T_{true} , and were outside with T_{false} .

Moreover in Figure 4, almost all 90% CI for means of the concentrations lied within the equivalence limit with T_{true} , and the 90% CI for means of the concentrations were outside the 90% equivalence interval with T_{false} .