Notes on the Design of Bioequivalence Study: Cycloserine

Notes on the design of bioequivalence studies are issued on planning and conducting such studies with products invited for submission to the WHO Prequalification Team: medicines (PQTm). Deviations from the approach suggested below can be considered acceptable if justified by sound scientific evidence.


Below, additional specific guidance is provided on the invited immediate release products, containing cycloserine.

**Pharmacokinetics of cycloserine**

There is contradictory information available on the pharmacokinetic properties of cycloserine. Whereas it has been reported that peak plasma concentrations are obtained 4 to 8 hours or 3 to 4 hours after administration of a dose of 250 mg, the information available for the PQTm suggests that tmax occurs within the first 3 hours after administration in fasting state. Similarly, the plasma half-life has been reported to be about 10–12 hours, but according to the information available for the PQTm the half-life is around 18 hours.

**Guidance for the design of bioequivalence studies**

Taking into account the pharmacokinetic properties of cycloserine, the following guidance with regard to the study design should be taken into account:

**Dose:** As cycloserine is marketed only as a 250 mg capsule, and the applied strength (i.e. 250 mg strength) should be employed in the bioequivalence study.

**Fasting/fed:** The bioequivalence study should be conducted in the fasting state as cycloserine can be taken irrespective of meals.

**Subjects:** Healthy adult subjects should be utilized. It is not necessary to include patients in the bioequivalence study.

**Analytical considerations:** The measurement of cycloserine is feasible (LLOQ of at least 5 ng/ml) and it is considered to be more discriminative to differences in the biopharmaceutical performance of the drug products. Bioequivalence should be based on the determination of cycloserine.
Sample size: Cycloserine pharmacokinetic parameters, Cmax and AUC0-t, in the fasting state seem to possess low to moderately variability (13–24%), based on information available to the PQTm. These data will facilitate the calculation of a sufficient sample size for the bioequivalence study.

Washout: Taking into account the elimination half-life of cycloserine of 18 h (range: 9–45 h), a washout period of 7 to 14 days is considered sufficient to prevent carryover.

Blood sampling: The blood sampling should be intensive for the first 3 hours after administration to properly characterize the Cmax of cycloserine. It is not necessary to take blood samples beyond 72 hours for the characterization of cycloserine pharmacokinetics.

Parent or metabolite data for assessment of bioequivalence: The parent drug is considered to best reflect the biopharmaceutical quality of the product. Bioequivalence should be based on the determination of cycloserine.

Statistical considerations: The data for cycloserine should meet the following bioequivalence standards in a single-dose, crossover design study:

- The 90% confidence interval of the relative mean AUC0-t of the test to reference product should be within 80–125%
- The 90% confidence interval of the relative mean Cmax of the test to reference product should be within 80–125%.