

Notes on the Design of Bioequivalence Study: Cycloserine

Notes on the design of bioequivalence studies with products invited for submission to the WHO Prequalification Unit – Medicines Assessment Team (PQT/MED) are issued to aid manufacturers with the development of their product dossier. Deviations from the approach suggested below can be considered acceptable if justified by sound scientific evidence.

The current notes should be read and followed in line with the general guidelines of submission of documentation for WHO prequalification. In particular, please consult the "Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability" in: *Fifty-first Report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Geneva, World Health Organization, 2017. WHO Technical Report Series, No. 1003, Annex 6.

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 PQT/MED suggests that t_{max} 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 PQT/MED 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:

Design: A single-dose cross-over design is recommended.

Dose: As the comparator product of cycloserine is marketed only as a 250 mg capsule, and the Expression of Interest includes cycloserine 250 mg capsule and 125 mg minicapsule, a study with the highest strength may suffice if the two strengths comply with the requirements for an additional strength biowaiver. Otherwise, two units of the 125 mg strength should be compared with one unit of the comparator 250 mg tablet in the bioequivalence study for the lower strength.

Fasted/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 recruited. It is not necessary to include patients in the bioequivalence study.

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

Sample size: Cycloserine pharmacokinetic parameters, C_{max} and AUC_{0-t} , in the fasted state seem to possess low to moderate variability (13–24%), based on information available to PQT/MED. These data may facilitate the calculation of a sufficient sample size for a single-dose cross-over 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 C_{max} of cycloserine. It is not necessary to take blood samples beyond 72 hours for the characterization of cycloserine pharmacokinetics.

Analytical considerations: The measurement of cycloserine is feasible (LLOQ of at least 5 ng/ml). The bioanalytical method should be sufficiently sensitive to detect concentrations that are 5% of the C_{max} in most profiles of each formulation (test or comparator).

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 AUC_{0-t} of the test to comparator product should be within 80.00 – 125.00%
- The 90% confidence interval of the relative mean C_{max} of the test to comparator product should be within 80.00 – 125.00%.