Notes on the Design of Bioequivalence Study: Alpha methyldopa

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. For guidance on issues related to bioequivalence (BE) studies for immediate-release, solid oral dosage forms, see the ICH Harmonised Guideline M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms (2024). For BE issues outside the scope of the ICH M13A guideline, e.g., for additional strength biowaivers, please consult the "Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability" in: *Fifty-seventh Report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Geneva, World Health Organization, 2024. WHO Technical Report Series, No. 1052, Annex 8.

Below, additional specific guidance is provided on the invited immediate release dosage forms containing alpha methyldopa.

Pharmacokinetics of alpha methyldopa

Peak concentrations in plasma occur at two to three hours, and elimination of the drug is biphasic regardless of the route of administration. Plasma half-life is 1.8 ± 0.2 hours according to the comparator products labelling, but other studies have shown values of 2.23 – 2.78 h.

Guidance for the design of bioequivalence studies

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

Design: A single-dose, crossover design is recommended.

Dose: As the EoI includes 250 mg tablets, this strength should be tested.

Fasted/fed: As the comparator product can be taken with or without food, a fasted state study is recommended.

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 alpha methyldopa.

Sample size: Information currently available to the PQT/MED indicates that the intra-subject variability for alpha methyldopa C_{max} is around 40% and 35% for AUC. These data will facilitate the calculation of sufficient sample size for the cross-over bioequivalence study.

Washout: Taking into account the elimination half-life of alpha methyldopa of 2 hours, a washout period of one week is considered sufficient to prevent carry over.

Blood sampling: As alpha methyldopa median t_{max} can range between 2 to 3, blood sampling should be intensive the first hours after administration to cover the peak of alpha methyldopa, e.g., pre-dose and at 0.25, 0.50, 0,75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.50, 4.00, 4.50, 6.00, 8.00, 12.00 and 16 hours post dose.

Analytical method: Information currently available to the PQT/MED indicates that it is possible to measure alpha methyldopa in human plasma using LC-MS/MS analytical methodology (LLOQ of 10 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). See Guideline on bioanalytical method validation and study sample analysis. In: WHO Technical Report Series, No. 1060, Annex 6, or the ICH Harmonised Guideline M10 for more information on bioanalytical recommendations.

Statistical considerations: The data for alpha methyldopa should meet the following bioequivalence standards in a single dose cross-over design study:

- The 90% confidence interval of the relative mean AUC_{0-t} of the test to reference product should be within 80-125%.

- The 90% confidence interval of the relative mean C_{max} of the test to reference product should be within 80-125%.

Biowaiver: A BCS-based biowaiver for alpha methyldopa is considered a possible alternative to a bioequivalence study, provided the requirements for granting a BCS-based biowaiver are met as outlined in the "WHO Guideline on Biopharmaceutics Classification System-based biowaivers" (2024) and the PQT/MED guidance "PQT/MED-specific Annotations for the WHO Guideline for Biopharmaceutics Classification System (BCS)-based Biowaiver Applications" (2025).