Notes on the design of bioequivalence study:
Sulfamethoxazole/Trimethoprim

Notes on the design of bioequivalence studies with products invited to be submitted to the WHO Prequalification Team – Medicines (PQTm) 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.


Below, additional specific guidance is provided on the invited immediate release products, containing sulfamethoxazole and trimethoprim.

Pharmacokinetics of sulfamethoxazole and trimethoprim

After oral administration trimethoprim and sulfamethoxazole are rapidly and nearly completely absorbed. The presence of food does not appear to delay absorption. Peak levels in the blood occur between one and four hours after ingestion and the level attained is dose related.

The half-life of trimethoprim in man is in the range 8.6 to 17 hours in the presence of normal renal function.

The half-life of sulfamethoxazole in man is approximately 9 to 11 hours in the presence of normal renal function.

Guidance for the design of bioequivalence studies:

Taking into account the pharmacokinetic properties of sulfamethoxazole and trimethoprim, the following guidance with regard to the study design should be considered:

Design: A cross-over design is recommended.

Dose: As the EoI includes Sulfamethoxazole /Trimethoprim tablets at the strengths of 400 mg/80 mg and 800 mg/160 mg, as well as in combination with Isoniazid /Pyridoxine at these same strengths, the highest strength of 800mg/160 mg is recommended for the bioequivalence study.

Fasting/fed: The bioequivalence study should be conducted in the fasting state.

Subjects: Healthy volunteers

Sample size: The intra-subject variability of Cmax of sulfamethoxazole and trimethoprim is approximately 18% and 14%, respectively. This data will facilitate the calculation of a sufficient sample size for the bioequivalence study.

Washout: 7 days at least.
**Blood sampling:** Predose and 0.25, 0.50, 1.00, 1.50, 2.00, 2.33, 2.67, 3.00, 3.33, 3.67, 4.00, 4.50, 5.00, 6.00, 8.00, 12.00, 18.00, 24.00, 30.00, 36.00, 48.00, and 72.00 hours after drug administration.

**Analytical considerations:** Information currently available indicates that it is possible to measure sulfamethoxazole and trimethoprim in human plasma using LC-MS/MS analytical methodology. 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).

**Parent or metabolite data for assessment of bioequivalence:** The parent drug is considered to best reflect the biopharmaceutical quality of the product. The data for the parent compound should be used to assess bioequivalence.

**Statistical considerations:** The data for sulfamethoxazole and trimethoprim 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%.