Notes on the design of bioequivalence study: Rifampicin

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 rifampicin.

Pharmacokinetics of rifampicin

Rifampicin is readily absorbed from the gastrointestinal tract. Peak serum concentrations occur about 2 to 4 hours after a single dose on an empty stomach. Absorption of rifampicin is reduced when the drug is ingested with food. In normal subjects the half-life of rifampicin in serum averages about 3 hours after a 600 mg dose and increases to 5.1 hours after a 900 mg dose.

Guidance for the design of bioequivalence studies:

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

**Design:** A cross-over design is recommended.

**Dose:** As the EoI includes 150 mg and 300 mg strengths, the 300 mg strength is recommended for the bioequivalence study when both strengths are developed and the 150 mg can be submitted as an additional strength biowaiver application.

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

**Subjects:** Healthy volunteers

**Sample size:** Rifampicin pharmacokinetic parameters, Cmax and AUC0-t, in the fasting state seem to possess low to moderate variability (10-27%), based on information available to the PQTm. These data will facilitate the calculation of a sufficient sample size for the bioequivalence study.

**Washout:** At least 7 days.

**Blood sampling:** Predose, 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 20.00, and 24.00 h after drug administration.
**Analytical considerations**: Information currently available indicates that it is possible to measure rifampicin in human plasma using LC-MS/MS analytical methodology. The bioanalytical method should be sufficiently sensitive to detect concentrations that are 5% of the $C_{\text{max}}$ 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 rifampicin 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 $C_{\text{max}}$ of the test to reference product should be within 80-125%.