Notes on the design of bioequivalence study: Rifampicin

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 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 by 30% 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. Rifampicin is to be taken 1 hour before or 2 hours after a meal.

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 single-dose cross-over design is recommended.

Dose: As the EoI includes 150 mg and 300 mg capsule 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.

Fasted/fed: The bioequivalence study should be conducted in the fasting state since rifampicin is to be taken on an empty stomach.

Subjects: Healthy volunteers 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. The data for the parent compound should be used to assess bioequivalence of rifampicin.

Sample size: Rifampicin pharmacokinetic parameters, C_{max} and AUC_{0-t}, in the fasting state seem to display low to moderate variability (10-27%), based on information available to the PQT/MED. These data will facilitate the calculation of a sufficient sample size for the cross-over bioequivalence study.

Washout: Taking into account the elimination half-life of rifampicin of 3 hours, a washout period of 7 days is considered sufficient to prevent carry-over.

Blood sampling: Blood samples should be collected at 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 to PQT/MED 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_{max} in most profiles of each formulation (test or comparator).

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