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. 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 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 crossover design is recommended.

Dose: The EoI includes 150 mg and 300 mg capsule or tablet strengths. A bioequivalence study should be conducted with the highest strength being developed, That is, the 300 mg strength should be employed for the bioequivalence study when both strengths of the capsule/tablet are developed and the 150 mg strength can be submitted as an additional strength biowaiver application, if the conditions for an additional strength biowaiver are fulfilled.

The EoI also includes 100 mg dispersible tablets. This strength should be employed in a bioequivalence study.

When conducting bioequivalence studies, it is essential to administer the test and the comparator product according to their corresponding instructions for use. In those cases where the test and the comparator product are different dosage forms with different methods of administration, the bioequivalence study should be conducted employing the intended method of administration of each product. For example, a dispersible tablet is typically dispersed in 30 – 50 mL of water prior to consumption and following consumption, the container might be rinsed with an additional small volume of water which is also consumed. Note that the total volume of water employed should not exceed 50 mL. For an oral suspension comparator product, the suspension should be prepared and administered as directed in its labelling. A small volume of water (30 – 50 mL) may be consumed after administration of the suspension if desired. Volumes of water greater than those mentioned above should not be employed for dispersible tablet or oral suspension products unless specifically indicated in the product labelling posology.

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 the 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: The blood sampling for rifampicin should be intensive the first four hours after administration to properly characterize the C_{max} of rifampicin. For example, samples should be collected at pre-dose, 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). 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 rifampicin 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 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%.