

Notes on the design of bioequivalence study: Raltegravir

Notes on the design of bioequivalence studies with products invited to be submitted 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 raltegravir.

Pharmacokinetics of raltegravir

In healthy volunteers administered single oral doses of raltegravir in the fasted state, raltegravir is rapidly absorbed with a t_{max} of approximately 3 hours post-dose. Raltegravir AUC and C_{max} increase dose proportionally over the dose range 100 mg to 1,600 mg.

Raltegravir may be administered with or without food. Food appears to increase pharmacokinetic variability relative to fasting.

The apparent terminal half-life of raltegravir is approximately 9 hours, with a shorter α -phase half-life (~1 hour) accounting for much of the AUC.

Guidance for the design of bioequivalence studies:

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

Design: A cross-over design is recommended.

Dose: The EoI includes 400 mg tablets. The bioequivalence should be conducted with a dose of 1 x 400 mg.

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

Subjects: Healthy volunteers

Sample size: Raltegravir pharmacokinetic parameters, C_{max} and AUC_{0-t} , in the fasting state seem to possess high variability (>30%), although information available is limited and confounding factors might have inflated the intra-subject variability estimation. A pilot study is recommended for a proper estimation of intra-subject variability until more data becomes available to PQT/MED. The pilot study data will facilitate the calculation of a sufficient sample size for the bioequivalence study.

Washout: At least seven (7) days.

Blood sampling: Predose, 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00 and 48.00 h after drug administration. The pilot study data will also facilitate the selection of the sampling time points.

Analytical considerations: Information currently available indicates that it is possible to measure raltegravir 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 raltegravir 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%.

Information currently available to PQT/MED suggests that the comparator product is a highly variable drug product for both AUC_{0-t} and C_{max} in the fasting state. Widening of the acceptance range for AUC_{0-t} is not acceptable, but the applicant may design a replicate cross-over study to estimate variability more accurately and to widen the acceptance range for C_{max} . For more information on replicate study designs and average scaled bioequivalence, refer to Annex 6, TRS 1003.