

## Notes on the Design of Bioequivalence Study: Efavirenz

Notes on the design of bioequivalence studies with products invited for submission to the WHO Prequalification Team – Medicines (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 efavirenz.

### **Pharmacokinetics of efavirenz**

Following oral administration, efavirenz peak plasma concentrations are typically reached within 5 h post-dose. Relative to fasting conditions, the administration of a single dose of efavirenz with a standardized high-fat meal increases the rate and extent of absorption of efavirenz. For this reason, efavirenz is to be administered on an empty stomach, preferably at bedtime.

Efavirenz is metabolized to a large extent via CYP3A and CYP2B6. The mean terminal half-life of efavirenz is 52–76 h following single doses and 40–55 h following multiple doses. Efavirenz is predominantly excreted via the bile and undergoes enterohepatic recycling.

Efavirenz appears to demonstrate non-linear pharmacokinetics with less than proportional increases in AUC observed with increasing dose, due to very limited solubility.

### **Guidance for the design of bioequivalence studies**

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

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

**Dose:** For APIs with non-linear pharmacokinetics within the range of strengths due to limited solubility of the API and resulting in less than proportional increases in AUC with increasing dose, bioequivalence studies should be conducted on at least the lowest strength (or a strength in the linear range) and the highest strength of a series of strengths.

The EoI includes Efavirenz 400 and 600 mg tablets only. Therefore, if both strengths are proposed, bioequivalence studies should be conducted with both strengths since a waiver is not possible between the 600 mg and the 400 mg strength due to less than proportional non-linear pharmacokinetics caused by limited solubility.

**Fasted/fed:** The bioequivalence study(ies) should be conducted in the fasted state.

**Subjects:** Healthy adult subjects 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. Therefore, bioequivalence should be based on the determination of efavirenz.

**Sample size:** Efavirenz is not a highly variable drug. Values for intra-subject %CV are generally 20–25% for  $C_{\max}$  and 10–15% for AUC. These data may facilitate the calculation of a sufficient sample size for a single-dose cross-over bioequivalence study.

**Washout:** Taking into account the elimination half-life of efavirenz in the fasted state of 52–76 h, a washout period of 28–35 days is considered sufficient to prevent carry over.

**Blood sampling:** The blood sampling should be intensive during the first 5 hours after administration to properly characterize the  $C_{\max}$  of efavirenz. Blood samples for the characterization of efavirenz pharmacokinetics should be taken for 72 h post-dose in order to determine truncated AUC values ( $AUC_{0-72h}$ ).

**Analytical considerations:** Information currently available to PQT/MED indicates that it is possible to measure efavirenz 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 efavirenz 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%.