Notes on the Design of Bioequivalence Study: Sofosbuvir

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.


Below, additional specific guidance is provided on the invited immediate release products containing sofosbuvir.

Pharmacokinetics of sofosbuvir
Following oral administration, sofosbuvir is absorbed quickly and the peak plasma concentration was observed ~0.5–2 hour(s) post-dose, irrespective of the dose level. Relative to fasting conditions, the administration of a single dose of sofosbuvir with a standardized high fat meal slows the rate of absorption of sofosbuvir. Further, with food, the extent of absorption of sofosbuvir is increased approximately 1.8-fold, with little effect on peak concentration. For this reason, administration is recommended with food in the Summary of Product Characteristics approved by the European Medicines Agency (EMA), although it can be taken irrespective of meals according to the Product Labelling approved by the US Food and Drug Administration (US FDA). The median terminal half-life of sofosbuvir is 0.4 hours.

Guidance for the design of bioequivalence studies
Taking into account the pharmacokinetic properties of sofosbuvir, 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 only the 400 mg tablet strength for sofosbuvir, this strength (i.e., 400 mg) should be employed in the bioequivalence study.

Fasted/fed: It is preferred that the bioequivalence study be conducted in the fed state with a high-fat high-calorie meal as sofosbuvir exhibits a greater absorption in the presence of a high-fat meal. However, as the approved labeling for the posology for Sovaldi, the WHO prequalification comparator product, differs between the EMA and the US FDA, a bioequivalence study conducted under fasted conditions will also be acceptable if the comparator product is obtained from a market where the approved labeling indicates that it may be taken without regard to food.

Subjects: Healthy adult subjects should be recruited. It is not necessary to include patients in the bioequivalence study.
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**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 sofosbuvir.

**Sample size:** Sofosbuvir $C_{\text{max}}$ in the fed state seems to be highly variable (54%), whereas $\text{AUC}_{0-t}$ seems to have low variability (10%), based on the information available to PQT/MED. These data may facilitate the calculation of a sufficient sample size for the cross-over bioequivalence study.

**Washout:** Taking into account the elimination half-life of sofosbuvir in fed state of 1.5 h (range: 0.3−9 h), a washout period of seven days is considered sufficient to prevent carry-over.

**Blood sampling:** The blood sampling should be intensive the first four hours after administration to properly characterize the $C_{\text{max}}$ of sofosbuvir. It is not necessary to take blood samples beyond 8−12 hours for the characterization of sofosbuvir pharmacokinetics.

**Analytical considerations:** Information currently available indicates that it is possible to measure sofosbuvir in human plasma using LC-MS/MS analytical methodology (LLOQ = 0.5 ng/ml). 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).

**Statistical considerations:**

The data for sofosbuvir should meet the following bioequivalence standards in a single-dose crossover design study:

- The 90% confidence interval of the relative mean $\text{AUC}_{0-t}$ of the test to reference product should be within 80.00−125.00%.

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

Information currently available to PQT/MED indicates that the comparator product is a highly variable drug product. Therefore, if the Applicant suspects that the variability of $C_{\text{max}}$ or $\text{AUC}_{0-t}$ is high (CV>30%), the applicant may prefer to employ a full replicate design study in order to widen the acceptance range of $C_{\text{max}}$ and/or $\text{AUC}_{0-t}$. For more information on replicate study designs and widening the limits of average bioequivalence, refer to Section 7.9.3 of Annex 6, TRS 1003 and PQT/MED guidance document “Application of reference-scaled criteria for AUC in bioequivalence studies conducted for submission to PQT/MED”.
