Notes on the Design of Bioequivalence Study: 
Zidovudine

Notes on the design of bioequivalence studies with products invited to be submitted to the WHO Prequalification Team – Medicines (PQTm) 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 zidovudine.

Pharmacokinetics of zidovudine

Zidovudine is well absorbed with peak serum concentrations occurring within 0.5 to 1.5 hours. Zidovudine may be administered with or without food. The extent of zidovudine absorption (AUC) was similar when a single dose of zidovudine was administered with food. The mean terminal plasma half-life was 1.1 hours.

Guidance for the design of bioequivalence studies

Taking into account the pharmacokinetic properties of zidovudine 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 zidovudine oral solution (50 mg/5ml), 300 mg tablets, and 250 mg capsules.

For the oral solution, a single dose of 250 or 300 mg should be administered. The bioequivalence study of the oral solution can be waived if the qualitative and quantitative composition of the excipients is similar to that of the comparator, i.e. maltitol (6.4 g / 10 ml). Preservatives (i.e. sodium benzoate), buffer agents (i.e. citric acid), and flavours (i.e. strawberry flavour and white sugar flavour) may differ.

The bioequivalence study for the tablets and capsules should be conducted with the corresponding strengths. The bioequivalence study for the tablet and the capsule could be waived according to the requirements for Biopharmaceutics Classification System (BCS) biowaivers since zidovudine is classified as BCS class I drug.

**Fasting/fed:** As zidovudine may be taken with or without food, a fasting state study is recommended.

**Subjects:** Healthy adult subjects should be utilized. It is not necessary to include patients in the bioequivalence study.
**Sample size:** Zidovudine $C_{\text{max}}$ seems to exhibit high variability, with approximately 31 – 36% intra-subject variability. These data may facilitate the calculation of a sufficient sample size for a cross-over bioequivalence study.

**Washout:** Taking into account the elimination half-life of zidovudine in healthy volunteers of 1.1 hours, a washout period of 7 days is considered sufficient to prevent carry over.

**Blood sampling:** The blood sampling should be intensive for the first hours after administration to properly characterize the $C_{\text{max}}$ of zidovudine. It is not necessary to take blood samples beyond 8 hours for the characterization of zidovudine pharmacokinetics. For example, samples can be taken pre-dose and at 0.17, 0.33, 0.50, 0.67, 0.83, 1.00, 1.25, 1.50, 1.75, 2.00, 2.5, 3.00, 4.00, 6.00 and 8.00 hours.

**Analytical considerations:** Information currently available indicates that it is possible to measure zidovudine in human plasma using LC-MS/MS analytical methodology. The bioanalytical method should be sufficiently sensitive to detect concentrations that are 5% of the $C_{\text{max}}$ 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 disposition of zidovudine should be characterized, and the determination of bioequivalence will be based on the parent compound.

**Statistical considerations:** The data for zidovudine 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 80–125%.
- The 90% confidence interval of the relative mean $C_{\text{max}}$ of the test to reference product should be within 80–125%.

Information currently available to the PQTm suggests that the comparator product might be a highly variable drug product for $C_{\text{max}}$, but not for $AUC_{0-t}$. Widening of the acceptance range for $C_{\text{max}}$ might be acceptable if the applicant conducts a replicate cross-over study to estimate variability of the comparator product more accurately and the high variability of $C_{\text{max}}$ is demonstrated. For more information on replicate study designs and scaled average bioequivalence refer to Section 7.9.3 of Annex 6, TRS 1003.