Notes on the Design of Bioequivalence Study:
Primaquine

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 suggestedbelow 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. WHO Technical Report Series 1003, 2017, Annex 6.

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

Pharmacokinetics of primaquine

Peak plasma concentrations occur about 1 to 3 hours after a dose is taken and then rapidly diminish with a reported elimination half-life of 7 hours (3.7 to 9.6 hours).

Taking primaquine after a meal may reduce abdominal pain or cramps associated with ingestion of the drug.

Guidance for the design of bioequivalence studies:

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

Design: A single-dose cross-over design is recommended. It is noted that a BCS-based biowaiver maybe possible if sufficient data can be collected to confirm primaquine as BCS Class I or III.

Dose: As the EoI includes primaquine 2.5, 5, 7.5 mg tablets, preferably dispersible for paediatric use, and 15 mg tablets, and the comparator product is marketed only as 15 mg tablets, the 15 mg strength should be tested in the bioequivalence study if the conditions for additional strength biowaivers are met. If these conditions are not met (e.g. if the 15 mg strength of the test product is not dispersible and differs from the paediatric dispersible tablets) bioequivalence studies should be conducted for each strength that do not fulfill these conditions (e.g. 2 units of the 7.5 mg dispersible test tablet *vs.* the 15 mg comparator tablet.

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 (e.g. a tablet that should be taken with a glass of water *vs.* a dispersible tablet to be dispersed in 30 – 50 mL of water) the bioequivalence study should be conducted employing the intended method of administration of each product. It is considered incorrect to standardize the volume of liquid in all these cases (e.g. administering a glass of water after the intake of a dispersible tablet or rinsing the container where a dispersible tablet has been suspended with the remaining liquid of a glass of water) because this standardization does not occur in real life conditions.

Fasted/fed: The bioequivalence study should be conducted in the fasted state as although it is generally taken after meals, this seems to be related to tolerability and not pharmacokinetics.

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. The data for the parent compound should be used to assess bioequivalence of primaquine.

Sample size: Limited information is available on primaquine variability. A pilot study is recommended to confirm the intra-subject variability and to explore the optimal sampling times.

Washout: Taking into account the elimination half-life of primaquine of 7 h, a wash out period of 1 week is recommended.

Blood sampling: The blood sampling should be intensive in the first 3 hours. It is not necessary to take samples after 24 hours. For example, blood samples might be taken at pre-dose and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.25, 2.5, 2.75, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 8.0, 10.0, 12.0, 16.0 and 24.0 h after drug administration.

Analytical considerations: Information currently available indicates that it is possible to measure primaquine 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 primaquine 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 comparator product should be within 80–125%

- The 90% confidence interval of the relative mean C_{max} of the test to comparator product should be within 80–125%.