

# Notes on the Design of Bioequivalence Study: Clindamycin

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.

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 clindamycin.

## Pharmacokinetics of clindamycin

About 90% of a dose of clindamycin hydrochloride is absorbed from the gastro-intestinal tract. Maximum concentrations are observed within one hour after administration. Absorption is not significantly diminished by food in the stomach, but the rate of absorption may be reduced. The half-life is 2 to 3 hours.

## Guidance for the design of bioequivalence studies

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

**Design:** A single-dose, crossover design is recommended.

**Dose:** As the EoI includes clindamycin tablets of 150 mg and 300 mg, the bioequivalence study should be conducted with the highest strength.

**Fasted/fed:** The bioequivalence study should be conducted in 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. The data for the parent compound should be used to assess bioequivalence of clindamycin.

**Sample size:** Information currently available to PQT/MED indicates that the intra-subject variability for clindamycin is around 20 – 30%. These data may facilitate the calculation of a sufficient sample size for the bioequivalence study.

**Washout:** Taking into account the elimination half-life of clindamycin of 2 – 3 h, a washout period of 7 days is considered sufficient to prevent carry-over.

**Blood sampling:** The blood sampling should be intensive for the first hour after administration to properly characterize the  $C_{\max}$  of clindamycin. For example, blood samples should be taken at pre-dose, 0, 17, 0.33, 0.50, 0.67, 0.83, 1.00, 1.25, 1.50, 2.00, 3.00, 4.00, 5.00, 6.00, 8.00, 10.00, 12.00 and 14.00 h after drug administration.

**Analytical considerations:** Information currently available to PQT/MED indicates that it is possible to measure clindamycin in human plasma using LC-MS/MS analytical methodology with a LLOQ of 50 ng/ml. 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 clindamycin 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 80.00–125.00%
- The 90% confidence interval of the relative mean  $C_{\max}$  of the test to reference product should be within 80.00– 125.00%.