

Notes on the Design of Bioequivalence Study: Dexamethasone

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 products containing dexamethasone.

Pharmacokinetics of dexamethasone

The pharmacokinetics of dexamethasone after intravenous administration are linear. A second peak after intravenous administration can be explained by enterohepatic recirculation. The disposition of dexamethasone is biexponential. After oral administration, the bioavailability is 76%. The maximum concentration is reached after 0.75 – 1.5 h (0.5 – 2.0 h) and the elimination half-life is 3.6 – 4.0 h. Dexamethasone should be taken with or after food to minimise irritation to the gastrointestinal tract.

Guidance for the design of bioequivalence studies

Taking into account the pharmacokinetic properties of dexamethasone, 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 dexamethasone 1.5 mg, 2 mg, and 6 mg tablets, the highest strength of the series to be developed should be administered. The bioequivalence study for the additional lower strengths may be waived if the conditions for an "additional strength biowaiver" are met with regard to manufacturing method, qualitative and quantitative composition, and similarity of the dissolution profiles. In the case of oral solutions, the EoI includes 2 mg / 5 ml and 10 mg / 5 ml (expressed as dexamethasone base). In this case, the bioequivalence study should be conducted with the 6 mg dose (i.e., 15 ml of 2 mg / 5 ml or 3 ml of 10 mg / 5 ml oral solutions).

Fasted/fed: Although dexamethasone is administered during or after meals to avoid gastrointestinal adverse effects, a single dose in healthy volunteers is considered to be tolerable. Therefore, the bioequivalence study should be conducted in the fasting state, since it is considered the most discriminative study condition.

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 dexamethasone.

Sample size: Dexamethasone C_{max} exhibits moderate intra-subject variability (18 – 21%), whereas AUC_{0-t} , exhibits low variability (9 – 13%) in the fasting state when administering a dose of 4 or 8 mg, based on information available in the literature¹⁻³. However, a study with intra-subject CV of 33% for C_{max} and 22% for AUC when administering a dose of 2 mg has been reported in the literature⁴. 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 dexamethasone in healthy volunteers of 4 hours, a washout period of seven days is considered sufficient to prevent carry over.

Blood sampling: The blood sampling should be intensive for the first two hours after administration to properly characterize the C_{max} of dexamethasone. For example, samples can be taken pre-dose and at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 4.00, 5.00, 8.00, 12.00, 16.00 and 24.00 h after drug administration.

Analytical method: Information currently available to PQT/MED indicates that it is possible to measure dexamethasone 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 dexamethasone 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%.

Waiver of the *in vivo* demonstration of bioequivalence

The Invitation to Manufacturers of therapeutics against COVID-19 to submit an EoI for product evaluation includes dexamethasone solution for injection, containing dexamethasone base 3.3 mg/ml or 6.6 mg/ml, as the sodium phosphate (equivalent to dexamethasone phosphate 4 mg/ml or 8 mg/ml, respectively). Multisource pharmaceutical products are considered to be equivalent without the need for further documentation when the pharmaceutical product is to be administered parenterally (e.g. intravenously, subcutaneously, or intramuscularly) as an aqueous solution containing the same API in the same molar concentration as the comparator product and the same or similar excipients in comparable concentrations to those in the comparator product. Certain excipients (e.g. buffer, preservative, and antioxidant) may be different provided it can be shown that the change(s) in these excipients would not affect the safety and/or efficacy of the pharmaceutical product.

The Invitation to Manufacturers of therapeutics against COVID-19 to submit an EoI for product evaluation includes dexamethasone oral solution, containing dexamethasone base 2 mg/5 ml or 10 mg/5 ml, as the base or sodium phosphate. Multisource pharmaceutical products are considered to be equivalent without the need for further documentation when pharmaceutically equivalent products are solutions for oral use (e.g. syrups, elixirs, and tinctures), contain the API in the same molar concentration as the comparator product, contain similar excipients in usual concentrations (if the API is BCS Class I) and the same excipients (i.e. cosolvents, surfactants, viscosity agents or critical excipients like sorbitol) in similar concentrations (for APIs from other BCS classes), although

buffers, flavours, colourants, antioxidants or preservatives may be changed. One of the presently authorised dexamethasone oral solutions in the UK, which may have been employed in the RECOVERY trial, is Martapan 2 mg / 5 ml oral solution. According to the SmPC of Martapan⁵, the amount of the critical excipients and cosolvent per 5 ml of oral solution are: 0.6 g of liquid sorbitol, 1.4 g of liquid maltitol and 0.5 g of Propylene glycol. This quantitative composition may serve as basis to obtain a waiver for the *in vivo* demonstration of bioequivalence oral solution irrespective of the BCS classification of dexamethasone, taking into account that the other excipients are preservatives (5 mg / 5 ml of Benzoic acid), flavours (Garden mint flavour (contains propylene glycol E1520)) and buffer agents (citric acid monohydrate, sodium citrate and citric acid 10% solution for pH adjustment), that might be changed without any expected impact on bioavailability. The quantitative composition of functional and critical excipients of the other dexamethasone oral solution marketed in UK does not seem to be publicly available. Therefore, a waiver based on that product is not feasible.

The Invitation to Manufacturers of therapeutics against COVID-19 to submit an EoI for product evaluation includes dexamethasone tablets, containing 1.5, 2, and 6 mg. Although at the maximum single therapeutic dose for other indications (e.g. 300 mg/day) dexamethasone (base) is classified as a low solubility drug, a BCS-based biowaiver approach might be accepted exceptionally if the indications for the applied product are limited to COVID-19, where the maximum single therapeutic dose is 6 mg. Therefore, if the Applicant demonstrates that the polymorph, if any, used in the applied product is the same as the morphic form used in the comparator product and the active pharmaceutical ingredient is highly soluble, according to the BCS criterion, based on a 6 mg dose, and stable, a BCS-based biowaiver would be acceptable, taking into account that the submitted information on permeability/absorption would impact the requirements on excipient composition and dissolution profile comparison since these requirements differ for BCS class I and III drugs. For a BCS-based biowaiver the same strengths of test and reference should be compared (i.e. 2 mg test tablet vs. 2 mg comparator tablet). In this exceptional case, for those strengths that are not available in the comparator product (i.e. 1.5 and 6 mg tablets), the dissolution profile comparison should be conducted not only with one tablet per vessel (e.g. 1 x 1.5 mg test tablet vs. 1 x 2 mg comparator tablet and 1 x 6 mg test tablet vs. 1 x 4 mg or 8 mg tablet), but also with the lowest common dose per vessel (e.g. 1 x 1.5 mg tablet vs. 3 x 0.5 mg comparator tablet and 1 x 6 mg test tablet vs. 3 x 2 mg comparator tablet).

In general, a BCS biowaiver for dexamethasone is considered a possible alternative to a bioequivalence study, provided the requirements for granting a BCS-based biowaiver are met as outlined in the ICH Guideline "*Biopharmaceutics Classification System-Based Biowaivers*" M9 (2019) and the PQT/MED guidance "*PQT/MED-specific Annotations for the ICH M9 Guideline for Biopharmaceutics Classification System (BCS)-based Biowaiver Applications*" (2021).

References:

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