DRAFT WORKING DOCUMENT FOR COMMENTS:

Inquiry regarding WHO product-specific guidance on the design of bioequivalence studies

Please send your comments to Dr Steve Estevão Cordeiro, Technical Officer, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (estevaos@who.int), with a copy to Ms Claire Vogel (vogelc@who.int) before 26 March 2021. Please use the “Table of Comments” document for this purpose.

Our working documents are sent out electronically and they will also be placed on the WHO Medicines website (https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/pharmaceuticals/current-projects) for comments under the “Working documents in public consultation” link. If you wish to receive all our draft guidelines, please send your email address to jonessi@who.int and your name will be added to our electronic mailing list.

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SCHEDULE FOR DRAFT WORKING DOCUMENT QAS/21.876:

Inquiry regarding WHO product-specific guidance on the design of bioequivalence studies

<table>
<thead>
<tr>
<th>Description of activity</th>
<th>Date</th>
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<td>The Fifty-fifth Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) recommended that the WHO Secretariat explore the feasibility of presenting product-specific guidance texts on how to design bioequivalence studies to the ECSPP with a view to making them more generally available to regulators.</td>
<td>October 2020</td>
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<tr>
<td>Preparation of first draft working document.</td>
<td>January 2021</td>
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<tr>
<td>Mailing of working document inviting comments and posting of the working document on the WHO website for public consultation.</td>
<td>February 2021</td>
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<td>Consolidation of comments received and review of feedback.</td>
<td>March 2021</td>
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<td>Discussion of the feedback received during a virtual meeting with an expert working group.</td>
<td>April-May 2021</td>
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<tr>
<td>Discussion during the annual consultation on regulatory guidance for multisource products between the WHO Norms and Standards for Pharmaceuticals Team and the WHO Prequalification of Medicines Team assessment group.</td>
<td>June-July 2021</td>
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<tr>
<td>Presentation to the Fifty-sixth meeting of the ECSPP.</td>
<td>October 2021</td>
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<td>Any other follow-up action as required.</td>
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Inquiry regarding WHO product-specific guidance on the design of bioequivalence studies

Background

During the Fifty-fifth World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP), Expert Committee members were updated on the annual consultation on Regulatory Guidance for Multisource Products between the WHO Norms and Standards for Pharmaceuticals Team and the Prequalification of Medicines Team – Assessment Group (PQTm) which took place as a virtual meeting in June 2020 due to the Coronavirus disease 2019 (COVID-19) pandemic. Further to this meeting, the group of experts suggested whether PQTm’s product-specific guidance texts on how to design bioequivalence studies could be presented to the ECSPP with a view to making them more widely available to regulators.

At present, the guidance developed by PQTm is uniquely meant for products contained in an Expression of Interest for Product Evaluation (EoI) with the sole purpose of helping manufacturers with their product development to meet the WHO Prequalification Programme standards. This guidance should not be understood as being enforceable as deviations can be considered acceptable if justified by sound scientific evidence and without prejudice of the compliance with existing requirements. Furthermore, these product-specific texts should always be read and followed in line with the general WHO guideline on Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability\(^1\) adopted at the Fifty-first meeting of the WHO ECSPP.

The Expert Committee asked the WHO Secretariat to explore the feasibility of the above-mentioned proposal, specifically to collect feedback and assess whether making such guidance widely available (in particular to regulators worldwide) would be welcomed and advantageous.

In view of the fact that these guidance texts are currently developed by the WHO Prequalification Programme, it was proposed to use the existing approach (namely the scope, such as products

document structure) as a basis for product-specific guidance documents on the design of bioequivalence studies to be recommended for implementation to WHO Member States and other parties.

In light of the above, feedback is being sought on:

- whether it would be advantageous to recommend these guidance texts to other audiences, namely national regulatory authorities, in addition to the relevant manufacturers;
- whether any modification to the structure-content of the existing document(s) is needed to meet the needs of other stakeholders and, if so, suggestions to be welcomed; and
- whether these guidance texts should preferably be developed for a specific group of medicines.²

Note: This is an inquiry document to find out how best to move forward and will not be published as an annex to the ECSPP report.

The outcome of this inquiry document will be reported to the Fifty-Sixth ECSPP in October 2021.

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An example of product-specific guidance on the design of bioequivalence studies developed by PQTm can be found as Annex 1 to this document for ease of reference. Further examples can be found here:


Annex 1

Notes on the design of bioequivalence study: dexamethasone

A WHO product-specific guidance on the design of bioequivalence studies may follow the structure-content, as suggested below, or may be appropriately modified based on the feedback received.

1. Pharmacokinetics of dexamethasone

1.1. 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.

2. 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:

2.1. Study design: A cross-over design is recommended.

2.2. 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 m
of 10 mg/5 ml oral solutions).

2.3. **Fasting/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.

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

2.5. **Sample size:** Dexamethasone $C_{\text{max}}$ exhibits moderate intra-subject variability (18 – 21%),
whereas $\text{AUC}_{0-t}$, exhibits low variability (9 - 13%) in the fasting state when administering a dose
of 4 or 8 mg, based on information available in the literature\(^1\)\(^-\)\(^3\). However, a study with intra-
subject CV of 33% for $C_{\text{max}}$ and 22% for $\text{AUC}$ when administering a dose of 2 mg has been
reported in the literature\(^4\). These data will facilitate the calculation of a sufficient sample size
for the bioequivalence study.

2.6. **Washout:** 7 days.

2.7. **Blood sampling:** Predose, 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.

2.8. **Analytical method:** Information currently available 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 $C_{\text{max}}$ in
most profiles of each formulation (test or comparator).

2.9. **Parent or metabolite data for assessment of bioequivalence:** The parent drug is considered to
best reflect the biopharmaceutical quality of the proposed product. The data for the parent
compound should be used to assess bioequivalence.
2.10. **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 $\text{AUC}_{0-t}$ of the test to reference product should be within 80–125%;
- The 90% confidence interval of the relative mean $\text{C}_{\text{max}}$ of the test to reference product should be within 80–125%.

2.11. **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).
References


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