**Checklist and abstract for bioequivalence studies and/or biowaivers - established active substance MAAs**

Version 1.0

Date effective: 19/OCT/2023

# Introduction

There are common pitfalls in regulatory submissions related to bioequivalence studies and proposed biowaivers. The purpose of this checklist is to remind applicants to submit information that is frequently omitted, and to promote ‘right first time’ submissions. The checklist may also empower companies to consider whether a submission package is likely to be approvable. Submission of this checklist is optional.

**Scope**: Submissions which include a bioequivalence study and/or a biowaiver for immediate release formulations with systemic action for established active substances.

**Action**: Applicants should complete this checklist and the ‘bioequivalence study abstract’ if appropriate, and submit as a ‘working document’ in Microsoft Word format in the initial sequence. The document should be titled ‘Bioequivalence\_Biowaiver\_Checklist\_Abstract’. A pdf version of the document should be submitted in Module 1 of the eCTD in the ‘m1-additional-data’ folder.

When selecting a ‘Yes/No’ option, if the option selected has red text with an asterisk (\*) this represents an approach which frequently requires additional justification:

* Please list these question numbers in the ‘additional comments’ section at the bottom of this document, providing brief justification.
* For some questions additional instructions are given in red text, as appropriate.

For options with a double asterisk (\*\*), please also provide full justification in the eCTD – usually in Module 1.5 or 2.5, although other Modules may sometimes be appropriate. In the ‘additional comments’ section at the bottom of this document, state the eCTD module where full justification is provided.

As a general note, the Clinical Overview should be used to describe and justify any deficiencies or irregularities in the submission, or deviations from the bioequivalence guideline (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr \*\*). These issues may be acceptable if adequately justified. Justification should be provided proactively in the initial submission, rather than in response to questions.

# Overview

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| --- | --- |
| 1. Product details | PL Number: <>  Name: <>  Active substance(s): <>  Strength(s): <>  Dosage form: <> |
| 2. Has a bioequivalence study been conducted to support this submission? | Yes/No  Study ID: <>  Full name of study: <>  Study sites (clinical, bioanalytical, PK/statistical analysis, sponsor): <>  Study dates: <>  [if multiple bioequivalence studies have been conducted, please list the above information for each study] |
| 3. Is a biowaiver proposed for some/all strengths? | Yes/No  Type of biowaiver proposed for each strength: <>  [Common biowaiver types include:   * ‘Additional strength biowaiver’, ‘oral solution biowaiver’, or ‘parenteral solution biowaiver’, as described in Bioequivalence Guidance (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr \*\*) * BCS-based biowaivers, as described in ICH M9.] |
| 4. If scientific advice has been given by the MHRA or other regulators, has a copy of advice been attached as Annex 5.14, as described in the Application Form? | Yes/No\*/’No scientific advice given’ |
| 5. If scientific advice has been given by the MHRA or other regulators, is the approach taken in full compliance with the advice given? | Yes/No\*\*/’No scientific advice given’ |
| 6. To the best of your knowledge, has the same+ product been assessed, or is it under assessment, by the MHRA or another international regulator?  +The term “same product" means same qualitative and quantitative composition in active substance(s) and having the same pharmaceutical form from applicants belonging to the same mother company or group of companies OR which are "licensees". | Yes\*/No  If yes, provide further details under ‘additional comments’ section below. The relevant sections of the application form should be completed. |
| 7. Do the MAAs include ‘new strengths’ of established active substances | Yes\*\*/No  If yes, justify in Module 2.5 whether the new strength fits the established posology of the active substance. The benefits of introducing the new strength, risks of medication error, and implications for the Risk Management Plan should also be considered. |

# Bioequivalence study checklist

*[Delete this entire section if no bioequivalence study has been conducted. If multiple bioequivalence studies have been conducted, please list this information for each study. The term ‘Bioequivalence Guidance’ in the below checklist refers to Bioequivalence Guidance (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr \*\*) unless otherwise specified]*

## Bioequivalence study - General

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| 8. Is the study in full compliance with Bioequivalence Guidance? | Yes/ No\*\* |
| 9. Is the study in full compliance with EMA product-specific bioequivalence guidance? | Yes/ No\*\*/’No product-specific guidance available’ |
| 10. Is the study in full compliance with ICH M10 | Yes/ No\*\* |
| 11. To the best of your knowledge, has this bioequivalence study been previously assessed or is it pending assessment by the MHRA or other regulators? | Yes\*/No  If yes, provide further details under ‘additional comments’ section below. The relevant sections of the application form should be completed. |
| 12. Referring to precedent from MHRA or EU public assessment reports for the same active substance, is the approach taken for the submitted bioequivalence study different from that previously accepted?  *(Consider factors such as strength investigated, fed vs fasting, whether defined as ‘narrow therapeutic index’, defining as ‘highly variable drug’, whether metabolites measured, whether enantiomers measured, or other.)* | Yes\*\*/No/’No precedent available’\*\*.  If yes or ‘no precedent available’, justify the approach in Module 1.5 or 2.5.  If no, please list examples here of previous procedures with the same active substance where this approach has been taken: <> |
| 13. Have methodology and results been summarised in Module 2.7.1 using the layout and content as detailed in Appendix IV of the Guideline on the Investigation on  Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1)? | Yes/No\*  Note that this is expected in all cases. Failure to provide Module 2.7.1 with layout and content in line with Appendix IV is likely to result in a subsequent request for this to be provided, and delays to assessment. |
| 14. Were multiple studies conducted for the same strength, due to at least one study failing to demonstrate bioequivalence? | Yes\*\*/No  Full study reports should be provided for all studies, except pilot studies for which study report synopses (in accordance with ICH E3) are sufficient.  At least one study must demonstrate bioequivalence independently. If one or more bioequivalence studies failed to demonstrate bioequivalence, the applicant should justify in Module 1.5 or 2.5 whether bioequivalence can still be concluded when considering the overall body of evidence. This justification could include a combined analysis of all studies. A combined analysis should use a model accounting for study, with each study considered as a separate group as described in below point on “if the study also included more than one group”. |

## Bioequivalence study - Specific

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| 15. Is the study a conventional, randomised, two-period, two-sequence, two-treatment, single dose crossover design? | Yes/No\*\*  If no, describe and justify the choice of study design in Module 1.5 or 2.5. Alternative designs may be acceptable, if fully justified in line with guidance. Note: some boxes within this checklist assume conventional single dose crossover design, and applicants may write ‘not applicable’ is appropriate. |
| 16. What was the study period? | Clinical: <xx/xxx/xxxx to xx/xxx/xxxx>  Bioanalytical: <xx/xxx/xxxx to xx/xxx/xxxx>  Ethics approval: xx/xxx/xxxx.  Ethics amendments: xx/xxx/xxxx  \*\*If ethics approval or amendments took place after initiation of the study, provide further information and justify whether this is acceptable. |
| 17. Was the study under fed or fasting conditions? | Fed/Fasting/both  If fed, has meal composition been described in the Clinical Study Report, and is it in line with the Bioequivalence Guidance?   * Yes/No\*\*/NA   If fed OR fasting OR both, is this approach in line with Bioequivalence Guidance, taking into consideration the product information of the reference and test product?   * Yes/No\*\* |
| 18. Is the test or reference product an oral solution? | Yes/No  If yes, is the administration of water in line with Question 3.7 of the ‘*Clinical pharmacology and pharmacokinetics: questions and answers*’?   * Yes/No\*\*/NA­­   If no, the proposed product information may require amendment to reflect the study methodology. |
| 19. Is the test or reference product an orodispersable tablet? | Yes/No  If yes, is the administration of water in line with Bioequivalence Guidance?   * Yes/No\*\*/NA   If no, the proposed product information may require amendment to reflect the study methodology. |
| 20. Is the substance being studied endogenous? | Yes\*\*/No  If yes, provide justification that study methodology and analysis is in line with Bioequivalence Guidance. |
| 21. Is the population studied in line with the Bioequivalence Guidance? | Yes/ No\*\* |
| 22. Have study site inspections (MHRA, EU, and other regulators) been listed in Table 2.2 of Module 2.7.1? | Yes/ No\*  Note that this is expected in all cases. Failure to provide Module 2.7.1 with layout and content in line with Appendix IV is likely to result in a subsequent request for this to be provided, and delays to assessment. |
| 23. Has a statement on the application of appropriate GCP standards in the submitted studies has been provided in the Clinical Study Report? | Yes/ No\*\* |
| 24. Is the Test Product composition and manufacturing process representative of that proposed for marketing? | Yes/ No\*\* |
| 25. Is the Bioequivalence Study Comparator Product chosen in line with the Bioequivalence Guidance or MHRA Guidance on comparator products? | Yes/ No\*\* |
| 26. Is the test product batch size at least 1/10 of production scale or 100,000 units, whichever is greater? | Yes/ No\*\* |
| 27. Is the assayed content of the batch used as test product no more than 5 % different to that of the batch used as reference product? | Yes/ No\*\* |
| 28. Is the maximum sample storage period from the first blood draw to the last analysis covered by long term stability data of the analyte? | Yes/ No\*\* |
| 29. Is the incurred sample reanalysis number in line with ICH M10?  *(As a minimum, if the total number of study samples is less than or equal to 1000, then 10% of the samples should be reanalysed; if the total number of samples is greater than 1000, then 10% of the first 1000 samples (100) plus 5% of the number of samples that exceed 1000 samples should be assessed.)* | Yes/ No\*\* |
| 30. Are primary and secondary pharmacokinetic variables in line with Bioequivalence Guidance? | Yes/ No\*\* |
| 31. Were Ln-transformed pharmacokinetic parameters Cmax and AUC(0-t) subjected to ANOVA for bioequivalence assessment? Were sequence, subject (sequence), period and formulation included as fixed effects in the ANOVA model?  Or if the study also included more than one ‘group’, were group, sequence, sequence\*group, subject (sequence\*group), period (group), and formulation included as fixed effects in the ANOVA model? (Note the model should **not** include a term for formulation\*group interaction). | Yes/ No\*\* |
| 32. Have the products been classified as narrow therapeutic index (NTI) for the purpose of BE acceptance intervals? | Yes/No  If yes, has it been justified in Module 1.5 or 2.5 whether Cmax is of particular importance for safety, efficacy or drug level monitoring, in line with Bioequivalence Guidance?   * Yes/No\*\*/NA   If no, is there regulatory precedent or literature precedent for describing the active substance as NTI?   * Yes/No/NA   If yes, has it been justified in Module 1.5 or 2.5 as to why the proposed product should not be classified as NTI for the purpose of BE acceptance intervals?   * + Yes/No\*\*/NA |
| 33. Was a replicate design used to widen Cmax acceptance intervals for a highly variable drug? | Yes/No  If yes, has the approach been justified in Module 1.5 or 2.5, including a sound clinical justification that wider difference in Cmax is considered clinically irrelevant?   * Yes/No\*\*/NA   If yes, have the widened limits for Cmax been calculated in line with Bioequivalence Guidance?   * Yes/No\*\*/NA |
| 34. Were any participant withdrawals or exclusions not in accordance with the study protocol? Were any decisions to exclude participants made after bioanalysis? | Yes\*\*/No |
| 35. Are plasma concentrations reported for each study subject for each treatment, including those who did not complete the study? | Yes/ No\*\* |
| 36. Have the appropriate subjects been included/excluded from the analysis?  *(Only subjects who provide evaluable data for both the test and reference product should be included. In a 2x2 study this means only subjects with data from both periods should be included. In a replicate study, subjects with missing periods should be included if they have one period with data for each product.*  *Some subjects - for example those withdrawn during Period 2 but after Cmax was recorded – should be included in the statistical analysis for Cmax, even if they cannot be included in the statistical analysis for AUC.*  *If the study has more than two treatment arms, the analysis for each comparison should exclude the data from the arms not included in the comparison.*  *The study report should make it easy to identify which subjects are included in the analysis, which periods were included, and the reasons for withdrawal.)* | Yes/ No\*\* |
| 37. Was pre-dose concentration >5% of the Cmax value for the subject in that period, in any subjects? | Yes\*\*/No  If yes, the statistical analysis should be performed with the data from that subject for that period excluded. Note: for endogenous substances, Bioequivalence Guidance should be followed. |
| 38. Was LLOQ <5% of the Cmax for all subjects in all periods? | Yes/ No\*\*  If no, this may be of concern, since one cannot ensure that pre-dose concentration is <5% of the Cmax value. Statistical analyses after exclusion of the relevant periods may be necessary, unless otherwise justified. |
| 39. Was extrapolated AUC more than 20% in more than 20% of observations?  *(Note that periods where the extrapolated area could not be calculated count as periods where the extrapolated area was more than 20%.)* | Yes\*\*/No  The validity of the study may need to be discussed, as described in Bioequivalence Guidance. |
| 40. Was Cmax observed in the first post-dose sampling time point in any subjects? | Yes\*\*/No  If yes, the validity of the study may need to be discussed if this occurs in a substantial proportion of periods, and/or if this may have affected the conclusion of bioequivalence. Additional statistical analyses may be necessary. |
| 41. Is there frequent enough sampling around Tmax to provide a reliable estimate of Cmax? | Yes/ No\*\* |
| 42.  Table: Bioequivalence evaluation, n=XXX   |  |  |  |  | | --- | --- | --- | --- | | **Study ID:** XXX | | | | | **Pharmacokinetic parameter** | **Geometric Mean Ratio Test/Ref** | **Confidence Intervals** | **CV%** | | Cmax (XXX/mL) | XXX.XX | XXX.XX - XXX.XX | XXX.XX | | AUC0-t (XXX \*hrs/mL)1 | XXX.XX | XXX.XX - XXX.XX | XXX.XX | | |
| 43. Did results for the primary PK parameters meet criteria for bioequivalence? | Yes/ No\*\* |
| 44. Were there any unexpected safety differences between the test and reference product? | Yes\*\*/No |
| 45. Are there any other atypical features of the study design or results which the applicant consider require discussion or justification? | Yes\*\*/No  As a general note, the Clinical Overview should be used to describe and justify any deficiencies or irregularities in the submission, or deviations from the guideline. These issues may be acceptable if adequately justified. Justification should be provided proactively in the initial submission, rather than in response to questions. |

# Biowaiver checklist

*[Delete this entire section if no biowaiver has been proposed. Delete subsections if a biowaiver of that type has not been proposed]*

## Additional strength biowaiver

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| 46. What is the linearity in pharmacokinetics of the active substance?  *(In order to assess linearity, the applicant may refer to the SmPC or Public Assessment Report of the Innovator Products, and/or may critically review literature data. For this purpose, linear PK is defined as when the difference in dose-adjusted mean AUCs is ≤25% when comparing the studied strength with the proposed biowaiver strengths.)* | Linear / Non-Linear with more than proportional increase in AUC with increasing dose / Non-Linear with less than proportional increase in AUC with increasing dose / Uncertain |
| 47. Has linearity in PK been discussed and justified in Module 1.5 or 2.5, as well as the choice of strength(s) for the bioequivalence study(ies)? Have the relevant primary literature references (e.g. to justify linearity) been provided in Module 5? | Yes/ No\*\* |
| 48. Given the linearity in pharmacokinetics of the active substance, has the bioequivalence study been conducted at the most appropriate strength(s) in line with Bioequivalence Guidance? | Yes/ No\*\* |
| 49. Have the general biowaiver criteria been met, and justified in Module 1.5 or 2.5 | Yes/ No\*\* |

## Oral solution biowaiver

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| --- | --- |
| 50. Is the test product an aqueous oral solution at time of administration containing an active substance in the same concentration as an approved reference medicinal product oral solution? | Yes/ No\*\* |
| 51. Has it been justified in Module 1.5 or 2.5 whether differences in excipients between the test and reference may affect bioavailability, in line with the Bioequivalence Guidance? | Yes/ No\*\* |

## Parenteral solution biowaiver’

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| 52. Has it been justified in Module 1.5 or 2.5 whether bioequivalence studies for the parenteral solution can be waived, in line with the Bioequivalence Guidance? | Yes/ No\*\* |

## BCS-based biowaiver

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| 53. Has it been justified in Module 1.5 or 2.5 whether the product meets the scope and the criteria for a BCS-based biowaiver, fully in line with ICH M9? | Yes/ No\*\* |
| 54. Referring to precedent from MHRA or EU public assessment reports for the same active substance, has a BCS-based biowaiver previously been accepted for the active substance? | Yes/ No\*\* |
| 55. BCS biowaiver eligibility criteria:  - Is the product an immediate release, solid orally administered dosage form or suspension designed to deliver drug to the systemic circulation?   - Is the drug product the same dosage form and strength as the reference product?   - Is the product non-narrow therapeutic index? | Yes/ No\*\*  If no to any question, the eligibility criteria stated in ICH M9 are not met. |
| 56. What is the ‘highest single therapeutic dose’? | Highest single therapeutic dose: <>  Has solubility been justified in line with ICH M9, at the highest single therapeutic dose?  Yes/ No\*\* |
| 57. Have the relevant primary literature papers (e.g. to justify permeability) been provided in Module 5? | Yes/ No\*\*  Please provide the relevant literature papers in Module 5. |
| 58. Have qualitative and quantitate comparisons of excipients between the test and reference product been provided, and are criteria met in line with ICH M9? | Yes/ No\*\* |
| 59. Have comparative *in vitro* dissolution data over the full range of pH stated in ICH M9 been provided, and are criteria met? | Yes/ No\*\* |

## Other biowaiver

|  |  |
| --- | --- |
| 60. For proposed biowaivers which do not exactly fit the above categories or guidelines, has the proposed approach been justified in Module 1.5 or 2.5? | Yes/ No\*\* |

# Additional comments

*For questions from the above checklist where the option selected has red text with an asterisk (\*) this represents an approach which frequently requires additional justification. Please list these question numbers in the ‘additional comments’ section below, providing brief justification. For options with a double asterisk (\*\*), please also state the eCTD module where the full justification is provided.*

|  |  |
| --- | --- |
| Question number | Brief justification, and reference to eCTD module with further justification if appropriate. |
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*In the following box, please add any additional comments considered relevant to the bioequivalence study or proposed biowaiver for the submission.*

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# Bioequivalence study abstract

*[Delete this entire section if no bioequivalence study has been conducted. If multiple bioequivalence studies have been conducted, please list this information for each study.]*

*[In the below abstract template text, blue text should be amended or deleted, and checked for accuracy. Black text should also be checked for accuracy, and amended or deleted if appropriate. Blue and black text should remain blue and black, respectively. If any options in the above Bioequivalence Study checklist were selected with red text, the below abstract template text should be amended as appropriate using red text to provide further information relevant to this issue.]*

|  |
| --- |
| **Applicant’s Abstract: Bioequivalence Study <Study ID xxxx>**  Full name of study: <xxxx>  Study sites: *(Table 2.2 of Module 2.7.1 should be copied here, including clinical / bioanalytical / PK / Statistical / Sponsor sites, and the inspection dates by UK / EU / International Regulatory Authorities)*  Study dates:   * Clinical: <xx/xxx/xxxx to xx/xxx/xxxx> * Bioanalytical: <xx/xxx/xxxx to xx/xxx/xxxx> * Ethics approval: <xx/xxx/xxxx> * Ethics amendments: xx/xxx/xxxx   The applicant states that the study was in full compliance with the Bioequivalence Guidance (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr \*\*) and ICH M10. The applicant states that the study was in full compliance with EMA product-specific bioequivalence guidance for <active substance>. A statement on the application of appropriate GCP standards has been provided in the Clinical Study Report.  **Study Design:**  An open-label, randomised, two-treatment, two-sequence, two-period, single-dose, crossover oral bioequivalence study comparing the test product <xxxx> with the reference product <xxxx>.  The study was performed under <fed/fasting> conditions, in line with Bioequivalence Guidance, since the proposed and reference SmPCs recommend <add relevant posology instructions here>.  Assignment of the treatments to the study participants was performed as per the randomisation schedule. The randomisation scheduled is included as Appendix <Appendix Number> to the Clinical Study Report. The study was open-label for participants and investigators. The bioanalyst <was / was not> kept blinded to the sequence of the administration of the Test and Reference products until the bio-analysis of the samples was completed.  After an overnight fast of <xxxx hours>, a <single oral dose> of either the test or the reference product was administered <with xxxx mL of drinking water>. A washout period of <xxxx days> was maintained between the successive dosing days.  As per the protocol, venous blood samples were drawn at <0.00 (pre-dose sample), xxxx, ….>. The sampling schedule was designed to reliably estimate the rate and the extent of exposure.  The Test Product and Comparator Product used in the study were as follows: *(Table 2.1 of Module 2.7.1 should be copied here)*  The Test Product composition and manufacturing process are representative of that proposed for marketing. The Comparator Product was chosen in line with <Bioequivalence Guidance / MHRA Guidance on comparator products>. The test product biobatch size was <xxxx>, whereas the maximum commercial batch size is <xxxx>. The test product biobatch size is at least 100,000 units and at least 10% of maximum commercial batch size. The difference between the assay values of the test (<xx%>) and the comparator product (<xx%>) was less than 5%. The Certificates of Analysis for the test and comparator products are located on <Page xxxx of Module xxxx>.  The population studied is chosen according to guidelines.  The bioanalytical method description/validation and the study sample analysis are in line with ICH Guideline M10 on bioanalytical method validation and are summarised in Module 2.7.1. The validated range is <xxxx-xxxx ng/ml >. The lower limit of quantitation (<xxxx ng/ml>) was <5% of the lowest individual Cmax (<xx ng/ml>). Higher quality control (<xxxx ng/ml>) was more than the maximum individual Cmax value (<xxxx ng/ml>).  *(Note: If LLOQ was not <5% of lowest individual Cmax, or HQC was not more than maximum individual Cmax, additional text should be added to describe in more detail and justify how this was managed).*  The maximum sample storage period from the first blood draw to the last analysis is <xxxx days> and <is / is not yet> covered by long term stability data of the analyte <(xxxx days at -xxxx°C)>. The incurred sample reanalysis number is <xxxx>, from the total number of study samples of <xxxx>, in line with ICH M10.  Primary and secondary pharmacokinetic variables are as follows, in line with Bioequivalence Guidance:  Primary Pharmacokinetic Parameters: <Cmax, AUC(0-t)>  Secondary Pharmacokinetic Parameters: <AUC(0-∞), tmax, t1/2, λz, AUC%extrapolated>  Ln-transformed pharmacokinetic parameters Cmax and AUC(0-t) were subjected to ANOVA for bioequivalence assessment, with sequence, subject (sequence), period and formulation included as fixed effects in the ANOVA model.  The active substance <is / is not> considered narrow-therapeutic index for the purpose of bioequivalence assessment. For the parametric analysis of bioequivalence for Ln-transformed data, the 90% confidence interval for the ratio of the test and reference products was to be contained within the acceptance boundaries of <80.00-125.00%> for Cmax, and <80.00-125.00%> for AUC(0-t) to conclude bioequivalence between treatments. This was prospectively defined.  <xxxx> subjects were included in the study, and <xxxx> subjects were randomised to receive the Test or the Reference Product. <xxxx> subjects did not complete the study, for the following reasons: *(please provide Subject IDs, reasons for not completing study, and timings of withdrawal relative to study period and dosing time).*  <xxxx> subjects were included in final statistical analysis of Cmax, and <xxxx> subjects were included in final statistical analysis of AUC.  Protocol deviations are listed in the Clinical Study Report. These are considered minor and unlikely to affect the study outcome. Actual blood sampling times were used for the calculation of PK parameters. All withdrawals were according to protocol. No decisions to exclude participants were made after bioanalysis.  Plasma concentrations are reported for each study subject for each treatment <Appendix Number>, including those who did not complete the study <Appendix Number>.  **Pharmacokinetic results:**  *(Table 3.1, 3.2, and 3.3 of Module 2.7.1 should be copied here.)*  *(Note: If, as per Table 3.2, any plasma concentration curves have AUC(0-t)/AUC(0-∞)<0.8, or Cmax as the first post-baseline point, or pre-dose sample >5% of Cmax, additional text should be added to describe in more detail and justify how this was managed).*  The results of the bioequivalence study <indicate / do not indicate> bioequivalence between the test and reference products for Cmax and AUC.  <There was no statistically significant formulation effect / sequence effect / period effect>. OR <The statistically significant formulation effect / sequence effect / period effect is not of concern given the study design and the results in line with accepted criteria for bioequivalence>.  There is no clear signal of any safety difference between the test and reference product, although this study was not powered to detect a difference in adverse events. |

# Checklist / abstract completed by:

Name:

Role:

Organisation:

Date:

Signature: