Rapporteur day 80 critical assessment report (Article 10.1 or 10.3)

Non clinical & clinical aspects – generic/hybrid medicinal products

<Invented name>

<(Active substance)>

EMEA/H/C/<XXX>

Applicant:

| CHMP Rapporteur: |  |
| --- | --- |
| <CHMP co-Rapporteur:> |  |
| EMA PL: |  |
| Start of the procedure: |  |
| Date of this report: |  |
| Deadline for comments: |  |

Note to the (Co)[Rapporteurs](https://www.ema.europa.eu/en/glossary/rapporteur" \o "One of the two members of a committee or working party who leads the evaluation of an application." \t "_blank): Assessment reports and comments should be circulated **VIA EUDRALINK**. Product Shared Mailbox: product.name-xxxx@ema.europa.eu and product initial MAA dedicated mailbox: MAAxxxx@ema.europa.eu (xxxx refers to the product number EMA/H/C/xxxx) should always be copied.

**Guidance text** is in green italics. You may print a copy of this template with the drafting note, then delete them all in one go:

Click on Ctrl-Alt-Shift-S to view the “styles” window. Select “Drafting notes (Agency)” and click on the icon on the right, chose “Select all XXX instances”, press the “Delete” key on the keyboard.

Do not change or delete the titles and the numbering style. (Add “Not applicable” if necessary)

Suggested font: Verdana 9.

Paragraph tab: alignment: left, outline level: body text, indentation: 0, spacing before: 0pt and after: 7pt; line spacing: at least, at: 14pt.

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Administrative information

|  |  |  |
| --- | --- | --- |
| **Invented name of the generic/hybrid medicinal product:** | |  |
| **INN (or common name) of the active substance(s):** | |  |
| **Active substance(s):** | |  |
| **Applicant:** | |  |
| **Applied Indication(s):** |  |
| **Pharmaco-therapeutic group**  **(ATC Code):** | |  |
| **Pharmaceutical form(s) and strength(s):** | |  |
| **CHMP Rapporteur contact person:**  **<CHMP Co-rapporteur contact person:>**  **EMA Product Lead:** | | **Name:**  Tel:  Email:  **Name:**  Tel:  Email:  **Name:**  Tel:  Email: |
| **Names of the CHMP Rapporteur assessors**  **(internal and external):** | | **Non-clinical:**  Name(s):  Tel:  Email:  **Clinical :**  Name(s):  Tel:  Email: |
| **<Names of the CHMP Co-Rapporteur assessors**  **(internal and external):>** | | **Non-clinical:**  Name(s):  Tel:  Email:  **Clinical:**  Name(s):  Tel:  Email: |

Declarations

The assessor confirms that this assessment does **not** include non-public information, including commercially confidential information (eg. ASMF, information shared by other competent authorities or organisations, reference to on-going assessments or development plans etc), irrespective from which entity was received\*.

*\*If the entity from which non-public information originates has consented to its further disclosure, the box should be ticked and there* would *be no need to add details below.*

Whenever the above box is un-ticked please indicate section and page where confidential information is located here:

List of abbreviations

GENERAL GUIDANCE

This template/guidance is for the initial assessment of generic/hybrid applications (legal basis Article 10.1 and 10.3 respectively) in the EU Centralised Procedure.

From a (non)clinical perspective, the primary basis for such assessment is usually the demonstration of bioequivalence. If, apart from bioequivalence studies, non-clinical data have been submitted for example to qualify impurities or to support the introduction of a new salt, a non-clinical assessment has to be performed. By analogy, additional clinical data may have been submitted (e.g. therapeutic equivalence studies) requiring a clinical assessment. In these cases the template should be supplemented with relevant headings from the respective templates of the Rapporteurs’ Day 80 assessment report for full initial Marketing Authorisation Applications.

Generic medicinal products under Article 10(1) of Directive 2001/83/EC are defined as having the same Qualitative and Quantitative composition in active substances and the same pharmaceutical form as a reference medicinal product and whose bioequivalence with the reference product has been demonstrated by appropriate bioequivalence studies.

The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regards to safety and/or efficacy. In such cases the, additional information providing proof of the safety and/or efficacy of the various salts, esters, or derivatives of an authorised active substance must be supplied by the applicant.

Also the purpose of an abridged application is to avoid the need for repetitive and unnecessary tests and trials (Recital 10 of Directive 2001/83 as amended which states that “there are reasons of public policy for not conducting repetitive tests on humans or animals without over-riding cause”.

Bioequivalence studies in humans studies may not be required if the applicant can demonstrate that the generic product meets relevant criteria for exemption as defined in appropriate detailed guidelines. [See Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98]

*Hybrid applications under Article 10(3) of Directive 2001/83/EC differ from generic applications in that the results of appropriate pre-clinical tests and clinical trials will be necessary in the following three circumstances:*

*• where the strict definition of a ‘generic medicinal product’ is not met;*

*• where the bioavailability studies cannot be used to demonstrate bioequivalence;*

*• where there are changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration of the generic product compared to the reference medicinal product*

*In such cases the results of tests and trials must be consistent with the data content standards required in the Annex to the Directive 2001/83/EC as amended by Directive 2003/63/EC. These applications will thus rely in part on the results of pre-clinical tests and clinical trials for a reference product and in part on new data.*

1. Type of application and other comments on the submitted dossier
   1. Orphan designation

<Not Applicable.>

or

Indicate if, and when the product received Orphan Drug Designation(s) related to the (applied) indication(s).Special consideration has to be given to orphan designated products with regard to the scope of the orphan condition in relation to the therapeutic indication claimed by the applicant (for a product to be authorised as an orphan medicinal product, the indication has to fall within the scope of the orphan designated condition).

<Product name> was designated as an orphan medicinal product EU/../../... on <date> in the following condition: <insert the orphan condition that relates to the indication in the MAA>.

*For extension(s) including new indication for an orphan product:*

< prod\_name >, was designated as an orphan medicinal product EU/../../... on <date> [include all designations and dates] in the following condition(s): <insert the orphan condition(s)>.

Please choose the appropriate paragraph below depending on whether the new therapeutic indication falls or does not fall within an existing orphan designation:

<The new indication, which is the subject of this application, falls within (one of) the above mentioned orphan designation(s).>

* 1. Similarity with orphan medicinal products

For all submissions, complete the following paragraph to reflect whether a similarity report was or was not submitted. If applicable, a separate AR on similarity is required (to be included as appendix).

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did <not> submit a critical report addressing the possible similarity with authorised orphan medicinal products <because there is no authorised orphan medicinal product for a condition related to the proposed indication>. <Assessment of these claims is appended.>

* 1. <Derogation(s) from orphan market exclusivity>

Complete the following paragraph only for submissions where claims for derogation(s) based on Art. 8.3 was/were submitted (i.e. where product is considered similar to an authorised orphan product). If applicable, a separate AR on the derogation(s) is required (to be included as appendix).

<The application contained a claim addressing the following derogation laid down in Article 8(3) of the Regulation (EC) No. 141/2000; <the holder of the marketing authorisation for the original orphan medicinal product has given his consent to the applicant> < the holder of the marketing authorisation for the original orphan medicinal product is unable to supply sufficient quantities of the medicinal product> <and> <the applicant can establish in the application that the medicinal product, although similar to the orphan medicinal product already authorised, is safer, more effective or otherwise clinically superior.> Assessment of these claims is appended.>

* 1. <Information on paediatric requirements>

1) Paediatric requirements apply only for art 10.3 applications as PUMA - Note: the Decision number below has a format P/X/XX. Do not mention the date.

<Pursuant to Article 30 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) [insert decision numbers] on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP *[insert decision number for the PIP eligible to the reward]* was completed.

<The PDCO issued an opinion on compliance for the PIP *[insert decision number for the PIP eligible to the reward]*.>

2) Paediatric requirements do not apply: If paediatric requirements do not apply at all to the concerned application, select the statement hereafter:

<Not applicable>

1. Non-clinical assessment

**FOR GENERIC/HYBRID APPLICATIONS WITHOUT NON-CLINICAL DATA**

The non-clinical assessment should be performed focused on the new information. Consider the paragraph below if no new non-clinical data have been submitted.

<A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable. >

Provide the conclusion by using one of the following two options:

<Pharmacodynamic, pharmacokinetic and toxicological properties of <ACTIVE SUBSTANCE> are well known. As <ACTIVE SUBSTANCE> is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.>

<The rapporteur considers that the non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is not adequate because /…/>

If the second option is chosen, provide a detailed description of the missing information, the impact this lack of information has, and any potential requests for additional data. This should then be translated into the draft list of questions (section 4).

In case a generic/hybrid contains a different salt, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of the active substance, include the appropriate statement:

<A summary of the literature with regard to non-clinical data of {medicinal product} and justifications that the different <salt><ester><ether><isomer><mixture of isomers><complex><derivative> of the active substance does not differ significantly in properties with regards to safety and efficacy of the reference product was <not>provided and was <not>accepted by the CHMP. This is <not> in accordance with the relevant guideline and additional non clinical studies were <not> considered necessary.>

**FOR GENERIC/HYBRID APPLICATIONS INCLUDING NON-CLINICAL DATA**

New non-clinical data might exceptionally have been submitted to qualify impurities, to support the introduction of a new salt, or because new non-clinical data have become available in the framework of an update or by clinical experience, e.g. regarding pregnancy, lactation, QT, etc, which may impact the SPC. In such case a new non- clinical assessment has to be performed. Points of interest such as recently published and clinically relevant animal data presented in the overview may be stated and commented here if necessary.

Use the relevant headings (Pharmacology, Pharmacokinetics, Toxicology) from the template of the Rapporteurs’ Day 80 non-clinical assessment report for full initial Marketing Authorisation Applications to describe such information. Also the assessment may have had an impact on the SmPC sections 4.6 and 5.3 (toxicology, mutagenicity, carcinogenicity, reproductive toxicity: teratogenicity, pregnancy, breastfeeding), which should be reflected hereunder.

* 1. <GLP aspects>

This section is only applicable for generic/hybrid applications including new data.

When new non-clinical data have been submitted, by example to qualify impurities, to support the introduction of a new salt, or because new non-clinical data have become available, e.g. regarding pregnancy, lactation, QT, etc, which may impact the SmPC, a new non-clinical assessment has to be performed. This chapter should be supplemented with relevant headings from the general templates of assessment report for non-clinical and clinical data.

Points of interest such as recently published and clinically relevant animal data presented in the overview may be stated and commented here if necessary.

Statements on GLP should be addressed here and also in the “overview module” of the assessment. This section is only required for applications including new data.

In this section specifically address:

Any concerns raised during the assessment about compliance with GLP requirements (data accuracy or protocol compliance). A useful tool to be used to identify the need for a triggered GLP inspection is the checklist “Triggers for audits of good laboratory practice (GLP)”

<http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2015/12/WC500199238.pdf>

Discuss the need for a GLP inspection.

To request a GLP inspection:

* Contact your national GLP monitoring authority.
* Contact EMA inspection sector - GLP inspection coordination.
* Determine with them the studies, sites and special concerns or issues related to the inspection.
* EMA inspection sector formulates the formal inspection request for review by the inspectors and agreement by the Rapporteur and Co-Rapporteur prior to adoption by CHMP (day 90 or 120).
  + 1. **<Pharmacology**
       1. Primary pharmacodynamic studies
       2. Secondary pharmacodynamic studies
       3. Safety pharmacology programme
       4. Pharmacodynamic drug interactions>
    2. **<Pharmacokinetics>**
    3. **<Toxicology**
       1. Single dose toxicity
       2. Repeat dose toxicity
       3. Genotoxicity
       4. Carcinogenicity
       5. Reproductive and developmental toxicity
       6. Toxicokinetic data
       7. Local tolerance
       8. Other toxicity studies>
  1. Ecotoxicity/environmental risk assessment

FOR ALL GENERIC/HYBRID APPLICATIONS THE SECTION “Ecotoxicity/environmental risk assessment” IS REQUIRED. Choose from one of the two options below.

FOR GENERIC/HYBRID APPLICATIONS WITHOUT ECOTOXICITY / ENVIROMENTAL DATA

<No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of <Product Name> manufactured by <Manufacturing Authorisation Holder> is considered unlikely to result in any significant increase in the combined sales volumes for all <active substance> containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.>

FOR GENERIC/HYBRID APPLICATIONS WITH ECOTOXICITY / ENVIROMENTAL DATA

**<Summary of main study results>**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Substance (INN/Invented Name):** | | | | | |
| **CAS-number (if available):** | | | | | |
| ***PBT screening*** |  | Result | | | **Conclusion** |
| *Bioaccumulation potential-* log *K*ow | OECD107 or … |  | | | Potential PBT (Y/N) |
| ***PBT-assessment*** | | | | | |
| **Parameter** | **Result relevant for conclusion** |  | | | **Conclusion** |
| Bioaccumulation | log *K*ow |  | | | B/not B |
| BCF |  | | | B/not B |
| Persistence | DT50 or ready biodegradability |  | | | P/not P |
| Toxicity | NOEC or CMR |  | | | T/not T |
| **PBT-statement :** | The compound is not considered as PBT nor vPvB  The compound is considered as vPvB  The compound is considered as PBT | | | | |
| ***Phase I*** | | | | | |
| ***Calculation*** | **Value** | **Unit** | | | **Conclusion** |
| PEC surfacewater , default or refined (e.g. prevalence, literature) |  | μg/L | | | > 0.01 threshold (Y/N) |
| Other concerns (e.g. chemical class) |  |  | | | (Y/N) |
| ***Phase II Physical-chemical properties and fate*** | | | | | |
| **Study type** | **Test protocol** | **Results** | | | **Remarks** |
| Adsorption-Desorption | OECD 106 or … | *K*oc = | | | List all values |
| Ready Biodegradability Test | OECD 301 |  | | |  |
| Aerobic and Anaerobic Transformation in Aquatic Sediment systems | OECD 308 | DT50, water =  DT50, sediment =  DT50, whole system =  % shifting to sediment = | | | Not required if readily biodegradable |
| ***Phase IIa Effect studies*** | | | | | |
| **Study type** | **Test protocol** | **Endpoint** | **value** | **Unit** | **Remarks** |
| Algae, Growth Inhibition Test/*Species* | OECD 201 | NOEC |  | µg/L | species |
| *Daphnia* sp*.* Reproduction Test | OECD 211 | NOEC |  | µg/L |  |
| Fish, Early Life Stage Toxicity Test/*Species* | OECD 210 | NOEC |  | µg/L | species |
| Activated Sludge, Respiration Inhibition Test | OECD 209 | EC |  | µg/L |  |
| ***Phase IIb Studies*** | | | | | |
| Bioaccumulation | OECD 305 | BCF |  | L/kg | %lipids: |
| Aerobic and anaerobic transformation in soil | OECD 307 | DT50  %CO2 |  |  | for all 4 soils |
| Soil Micro organisms: Nitrogen Transformation Test | OECD 216 | %effect |  | mg/kg |  |
| Terrestrial Plants, Growth Test/*Species* | OECD 208 | NOEC |  | mg/kg |  |
| Earthworm, Acute Toxicity Tests | OECD 207 | NOEC |  | mg/kg |  |
| Collembola, Reproduction Test | ISO 11267 | NOEC |  | mg/kg |  |
| Sediment dwelling organism |  | NOEC |  | mg/kg | species |

* 1. Assessor’s comment

Are the non-clinical sections of the SmPC acceptable?

If there are additional non-clinical data, are these data adequately reflected in the SmPC?

Grounds for non-providing new data justified adequately.

In most cases it is not necessary to include such comments.

* 1. Conclusions on non-clinical aspects

In case new non-clinical data was provided conclude on these data. Also conclude on the environmental risk assessment.

State if the SmPC of a generic product is identical to the reference product. Normally it should be, but any differences should be mentioned here. State whether the differences are justified or not.

State those issues that need to be clarified. These should be carried forward to the benefit risk assessment in the Clinical part of this report and listed in the List of Questions as appropriate.

Provide the conclusion by using one of the following two options:

<There are no objections to approval of <TRADE NAME> from a non-clinical point of view.>

*OR*

<As stated above, there are issues that need to be clarified, see list of questions.>

<The (Co-)Rapporteur considers the following measures necessary to address the non-clinical issues:>

1. Clinical assessment

*If, apart from bioequivalence studies, other clinical data have been submitted, this section should be supplemented with relevant subsections from the full application CHMP template.*

* 1. Introduction

Describe the Product profile: Indications and dosage (SmPC sections 4.1 and 4.2), pharmacodynamics and pharmacokinetics of the active substance PK summary of substance and formulation; absorption, distribution, metabolism, elimination data of special interest in respect of bioequivalence studies (linearity, elimination time etc.)(see e.g. text books such as Goodman & Gilman, Martindale etc).

Relevant for the assessment <is><are> the <Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1)> <as well as the><Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev.1)><Guideline on the pharmacokinetic and clinical evaluation of modified-release dosage forms (EMA/CHMP/EWP/280/96 Rev.1)><Question number <NUMBER> of the Questions & Answers: Positions on specific questions addressed to the  
Pharmacokinetics Working Party (EMA/618604/2008)>.

<The applicant did <not> receive CHMP Scientific Advice pertinent to the clinical investigation. <This advice concerned the following topics: [PROVIDE SUMMARY]. The applicant did <not> follow this scientific advice.>

* + 1. GCP aspects

GCP aspects (general)

In this section specifically address:

* Any concerns raised during the assessment about compliance with GCP or related regulatory and ethical requirements (data accuracy or protocol compliance and compliance with ethical aspects).
* Statement on application of ethical standards in clinical trials, where appropriate (Art 8 (ia) of the Directive; Art 9.4(c) and Art 127 (a) of the Regulation): "The applicant has to provide a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.".
* Discuss the need for a GCP inspection. Detailed information on triggers for inspection can be found in the document “Guidance on triggers for inspections of bioequivalence trials: Quick scan” prepared by the GCP Inspectors Working Group (GCP IWG) / Co-ordination Group for Mutual Recognition & Decentralised Procedures - Human (CMDh) on the EMA website [<http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2013/08/WC500148195.pdf>].

GCP aspects of Human Bioequivalence studies

Bioequivalence studies are normally the sole clinical studies provided with an application for a standard generic product. Careful consideration should be given to the need for a GCP inspection of the clinical and laboratory phases of the bioequivalence study. Particular points to consider include:

* Has the clinical site been inspected previously by EU inspectors?
* Has the laboratory site been inspected previously by EU inspectors?

This information should have been provided or will be sought by EMA. Are there issues that may act as triggers for inspection? e.g.:

* Lack of inspection experience with the site
* Indications from the dossier that there may be problems with the analytical laboratory analysis or with the clinical conduct of the study.
* Location of the clinical and laboratory sites

To request a GCP inspection:

* Contact your local GCP inspectorate.
* Contact EMA inspection coordinator - GCP inspection coordination.

Determine with them the clinical trial(s), sites and special concerns or issues to be addressed/the inspection. EMA inspection coordinator formulates the formal inspection request for review by the inspectors and agreement by the CHMP Rapporteur(s) prior to adoption by CHMP (day 90 or 120). If an inspection is requested the following wording should be added:

*[For routine GGP inspections]*

<A request for GCP inspection has been adopted for the following clinical study(ies) <enter study number(s)>. The outcome of this inspection and the satisfactory responses to its findings are an integral part of this procedure and will be needed by Day 181.>

And/or

*[For triggered GCP inspections]*

<A request for GCP inspection has been adopted for the following clinical study(ies) <enter study number(s)>. The outcome of this inspection and the satisfactory responses to its findings are part of the responses to the LoQ and will be needed by Day 121.>

* 1. Exemption

In this section describe two different kinds of biowaiver:

* exemption for strength(s)
* BCS-based Biowaiver

Refer to the respective requirements of the applicable Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98).

Also this section should be used to justify an exemption from the requirement to perform bioequivalence studies for e.g. certain dosage forms in accordance with the above-mentioned guideline.

* 1. Clinical pharmacology
     1. Introduction

To support the application, the applicant has submitted <NUMBER> bioequivalence study(ies), <NUMBER> pharmacodynanic studies, <NUMBER > therapeutic equivalence studies.

State the reasons for submitting more than one bioequivalence trial. If there is more than one clinical study, each of them should be described separately using the below structure.

Table 1. Tabular overview of clinical studies

* + 1. Pharmacokinetics

Study <Number>: <Title>

Methods

* Study design

Detailed description of the study design including drug intake procedures (fasting state or with food), meals served, fed/fasted condition, constituents of meal (in fed studies), multiple/single dose, applied dose, wash-out period, blinding, crossing-over, randomization, sampling schedule, analysed compound (parent and/or metabolites) and matrix (plasma, urine data).

In case of a steady-state study, relevant details (multiple dosing).

Information about investigator, study site, protocol number, study duration, bioanalysis facility, biostatistician and/or biostatistical institute.

Critical assessment of the adequateness of the study design.

Assessor’s comment

* Test and reference products

Detailed information of the reference product (name) strength, pharmaceutical form, MAH, date of authorisation in EU and the detailed information (such as MA batch number and country of origin) of the batches used in the studies need to be provided in tabular format. The following information should be included: Actual strength vs. nominal strength of the test and reference products employed in the bioequivalence study, batch size of the test product employed in the bioequivalence study and commercial batch size.

Assessor’s comment

The assessment should address if required data were given, if the test product is identical to the formulation intended to be marketed.

* Population(s) studied

Description of number of subjects included in the study, number of subjects included in PK- and statistical analysis, drop-outs (reason why in detail), ethnicity, gender, age, BMI, health status, etcetera

Assessor’s comment

The assessment should address if population chosen is according to guidelines, inclusion/exclusion criteria ok, sample size calculation ok, ethnicity, gender, age, BMI, health status, etc. Assess potential protocol deviations/violations.

* Analytical methods

Detailed description of analytical methods used, with emphasis on the performance characteristics of assay validation and quality control.

Provide all details relevant for the assessment of the validity of the bioanalytical method in accordance with the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/2009).

Assessor’s comment

Address if the analytical method is acceptable, validated, handling of samples adequate. Assess potential protocol deviations/violations.

* Pharmacokinetic variables

Summarise Pharmacokinetic variables and their generation (Non- compartmental/compartmental, PK analysis software. Choice of primary and secondary variables)

Assess if Pharmacokinetic variables and methods were adequate.

Assessor’s comment

* Statistical methods

Description of statistical methods including prospectively defined acceptance criteria.

Assessor’s comment

Assess if the statistics described were adequate, methods acceptable (transformations, parametric tests, handling of missing values, outliers, basis of bioequivalence, whether there were protocol deviations/violations and if any widening of the acceptance criteria has been adequately justified).

* Results

Summarise the relevant data for the bioequivalence assessment in the below tables rather than copying detailed statistical outputs from the clinical study report.

**Table X** **Pharmacokinetic parameters for <analyte> (non-transformed values)**

| **Pharmacokinetic parameter** | **Test** | | **Reference** | |
| --- | --- | --- | --- | --- |
| **<arithmetic> <geometric> mean** | **<SD> <CV%>** | **<arithmetic> <geometric> mean** | **<SD> <CV%>** |
| <AUC(0-t) ><AUC(0-72h) > |  |  |  |  |
| AUC(0-∞) |  |  |  |  |
| Cmax |  |  |  |  |
| Tmax\* |  |  |  |  |
| <AUC0-t area under the plasma concentration-time curve from time zero to t hours>  <AUC0-72h area under the plasma concentration-time curve from time zero to 72 hours>  AUC0-∞ area under the plasma concentration-time curve from time zero to infinity  Cmax maximum plasma concentration  Tmax time for maximum concentration (\* median, range) | | | | |

**Table X Statistical analysis for <analyte> (ln-transformed values)**

| **Pharmacokinetic parameter** | **Geometric Mean Ratio Test/Reference** | **Confidence Intervals** | **CV%\*** |
| --- | --- | --- | --- |
| <AUC(0-t) ><AUC(0-72h) > |  |  |  |
| Cmax |  |  |  |
| \* estimated from the Residual Mean Squares | | | |

In case steady state studies have been performed, similar tables should be produced reporting the parameters AUC0-t, Cmax, Cmin, and fluctuation index (PTF%).

Assessor’s comment

The assessment should address if the bioequivalence is shown appropriately. It should be assessed if Cmax is observed in any subject in the first sample time point; detectable pre-dose plasma levels, extrapolated AUC, etc.

* Safety data

Provide a very brief summary of the adverse events observed in the bioequivalence study.

Assessor’s comment

No conclusion in terms of comparison between test and reference should be made based on these data.

* + 1. Pharmacodynamics

<No new pharmacodynamic studies were presented and no such studies are required for this application.>

If applicable, usually no new data required and given. Required, if bioequivalence cannot be shown by pharmacokinetic studies in order to substantiate therapeutic equivalence.

Assessor’s comment

* 1. <Clinical efficacy>

*Consider this section ONLY for hybrid application where pivotal efficacy and safety studies were submitted. For the guidance please refer to the one for full marketing authorisation procedures.*

* + 1. Dose response study(ies)
    2. Main study/ies

<Title of Study>

Methods

* Study Participants
* Treatments
* Objectives
* Outcomes/endpoints
* Sample size
* Randomisation and Blinding (masking)
* Statistical methods

Results

* Participant flow
* Recruitment

Randomized (n= )

Assessed for eligibility (n= )

Excluded (n= )

♦  Not meeting inclusion criteria (n= )

♦  Declined to participate (n= )

♦  Other reasons (n= )

Analysed (n= )  
♦ Excluded from analysis (give reasons) (n= )

Lost to follow-up (give reasons) (n= )

Discontinued intervention (give reasons) (n= )

Allocated to intervention (n= )

♦ Received allocated intervention (n= )

♦ Did not receive allocated intervention (give reasons) (n= )

Lost to follow-up (give reasons) (n= )

Discontinued intervention (give reasons) (n= )

Allocated to intervention (n= )

♦ Received allocated intervention (n= )

♦ Did not receive allocated intervention (give reasons) (n= )

Analysed (n= )  
♦ Excluded from analysis (give reasons) (n= )

***Allocation***

***Analysis***

***Follow-Up***

***Enrollment***

* Conduct of the study
* Baseline data
* Numbers analysed
* Outcomes and estimation
* Ancillary analyses
  + 1. Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

**Table XXX**. Summary of Efficacy for trial <trial>

| **Title:** <title> *{as indicated on the study report}* | | | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study identifier | <code>  *{list all codes starting with the protocol number followed by – as available - EudraCT number, ISRCT number, other codes that allow cross-referencing to publications}* | | | | | | | | |
| Design | <free text>  *{describe key elements of the design (cross-over, parallel, factorial, dose-escalation, fixed-dose response) including randomization, blinding, allocation concealment, mono-/multi-centre, etc.}* | | | | | | | | |
| Duration of main phase: | | | | | <time> | | | |
| Duration of Run-in phase: | | | | | <time> <not applicable> | | | |
| Duration of Extension phase: | | | | | <time> <not applicable> | | | |
| Hypothesis | <Superiority> < Equivalence> <Non-inferiority> <Exploratory: specify> | | | | | | | | |
| Treatments groups  *{add as many rows as needed to describe the treatment groups}* | <group descriptor> *{provide abbreviation for use later in the table of the results section}* | | | | | <treatment>. <duration>, <number randomized> | | | |
| <group descriptor> | | | | | <treatment>. <duration>, <number randomized> | | | |
| <group descriptor> | | | | | <treatment>. <duration>, <number randomized> | | | |
| Endpoints and definitions *{add as many rows as needed to describe the endpoints; for the secondary endpoints select the ones considered most relevant and reported in the results section}* | <Co->Primary endpoint | | <label> *{generate abbreviation for use later in the table of the results section}* | | | <free text> *{provide brief description}* | | | |
| <Secondary> <other: specify> endpoint | | <label> | | | <free text> *{provide brief description}* | | | |
| <Secondary> <other: specify> endpoint | | <label> | | | <free text> *{provide brief description}* | | | |
| Database lock | <date> | | | | | | | | |
| **Results and Analysis** *{present the result separate for each analysis that is considered relevant for the conclusion on the trial; in any case the pre-specified primary analysis should be presented}* | | | | | | | | | |
| **Analysis description** | | **Primary Analysis** | | | | | | | |
| Analysis population and time point description | | <Intent to treat> <Per protocol> <other: specify>  *{consider adding a brief description of the definition of the population}*  <time point> | | | | | | | |
| Descriptive statistics and estimate variability | | Treatment group | | <group descriptor>  *{as per above terminology}* | | | <group descriptor>  *{as per above terminology}* | | <group descriptor>  *{as per above terminology}* |
|  | | Number of subject | | <n> | | | <n> | | <n> |
| <endpoint> *{label as above}*  (<statistic>) *{e.g. mean, median, etc}* | | <point estimate> | | | <point estimate> | | <point estimate> |
| <variability statistic> *{e.g. standard deviation, confidence interval, etc}* | | <variability> | | | <variability> | | <variability> |
| <endpoint>  (<statistic>) | | <point estimate> | | | <point estimate> | | <point estimate> |
| <variability statistic> | | <variability> | | | <variability> | | <variability> |
| <endpoint>  (<statistic>) | | <point estimate> | | | <point estimate> | | <point estimate> |
| <variability statistic> | | <variability> | | | <variability> | | <variability> |
| Effect estimate per comparison *{add as many rows as needed to describe the relevant statistical testing performed}* | | <Co->Primary endpoint | | | Comparison groups | | | <group descriptors>  *{as per above terminology}* | |
|  | |  | | | <test statistic> *{e.g. difference between groups}* | | | <point estimate> | |
| <variability statistic> *{e.g. confidence interval, etc}* | | | <variability> | |
| P-value*{indicate statistical test used, e.g. ANOVA}* | | | <P-value> | |
| <<Co->Primary > <Secondary><other: specify> endpoint *{indicate endpoint using terminology as per section “Endpoint and definitions}* | | | Comparison groups | | | <group descriptors> | |
| <test statistic> | | | <point estimate> | |
| <variability statistic> | | | <variability> | |
| P-value | | | <P-value> | |
| <<Co->Primary > <Secondary><other: specify> endpoint | | | Comparison groups | | | <group descriptors> | |
| <test statistic> | | | <point estimate> | |
| <variability statistic> | | | <variability> | |
| P-value | | | <P-value> | |
| Notes | | <free text> *{consider amongst others the following information:*  *- reasons for drop-outs*  *- critical findings with regard to the analysis}* | | | | | | | |
| **Analysis description** | | **<Secondary analysis> <Co-primary Analysis> <Other, specify: >** *{also indicate if the conduct of the analysis was pre-specified}* | | | | | | | |
| *{repeat all the above sections for each analysis that is considered relevant}* | |  | | | | | | | |

* + 1. <Clinical studies in special populations>

|  | Age 65-74 (Older subjects number /total number) | Age 75-84 (Older subjects number /total number) | Age 85+ (Older subjects number /total number) |
| --- | --- | --- | --- |
| Controlled Trials |  |  |  |
| Non Controlled trials |  |  |  |

* + 1. <In vitro biomarker test for patient selection for efficacy>
    2. <Analysis performed across trials (pooled analyses and meta-analysis)>
  1. <Clinical safety>

*Consider this section ONLY for hybrid application where pivotal efficacy and safety studies were submitted. For the guidance please refer to the one for initial MAA procedures.*

* + 1. Patient exposure
    2. Adverse events
    3. Serious adverse event/deaths/other significant events
    4. Laboratory findings
    5. In vitro biomarker test for patient selection for safety
    6. Safety in special populations

| **MedDRA Terms** | **Age <65**  **number (percentage)** | **Age 65-74**  **number (percentage)** | **Age 75-84**  **number (percentage)** | **Age 85+**  **number (percentage)** |
| --- | --- | --- | --- | --- |
| Total AEs |  |  |  |  |
| Serious AEs – Total |  |  |  |  |
| - Fatal |  |  |  |  |
| - Hospitalization/prolong existing hospitalization |  |  |  |  |
| - Life-threatening |  |  |  |  |
| - Disability/incapacity |  |  |  |  |
| - Other (medically significant) |  |  |  |  |
| AE leading to drop-out |  |  |  |  |
| Psychiatric disorders |  |  |  |  |
| Nervous system disorders |  |  |  |  |
| Accidents and injuries |  |  |  |  |
| Cardiac disorders |  |  |  |  |
| Vascular disorders |  |  |  |  |
| Cerebrovascular disorders |  |  |  |  |
| Infections and infestations |  |  |  |  |
| Anticholinergic syndrome |  |  |  |  |
| Quality of life decreased |  |  |  |  |
| Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures |  |  |  |  |
| <other AE appearing more frequently in older patients> |  |  |  |  |

* + 1. Immunological events
    2. Safety related to drug-drug interactions and other interactions
    3. Discontinuation due to adverse events
  1. Post marketing experience

Consider any evaluation of the safety data submitted (if the product has already been on the market elsewhere outside EU). However this is rarely available; Note that this information relates to the medicinal product and not the active substance.)

The following case is more likely:

<No post-marketing data are available. The medicinal product has not been marketed in any country.>

Assessor’s comment

* 1. Discussion on clinical aspects

Discuss critical design elements particularly if different from the standard cross-over design, e.g. parallel design, fed versus fasting state, investigation in patients, etc. Any relevant of the analyte (parent versus metabolite) as well as the bioanalytical method should be discussed. Also reflect on the pre-specified acceptance criteria for bioequivalence, particularly if scaling is applied for highly variable drugs (e.g. has a replicate design been employed to estimate the CV?) or for narrow therapeutic index drugs.

For the results, state whether the pre-set bioequivalence criteria where met. Also summarise any issues with regard to the conduct of the study (e.g. withdrawals/replacement of subjects). In case of conduct of more than study against the EU reference product, assess the conclusiveness of the available data.

Any concerns with regard to the GCP compliance of the study should be clearly described and discussed.

In case efficacy issues have been identified for inclusion in Annex II as conditions, it needs to be motivated in the CHMP AR, notably it should be explained in the context of a positive benefit/risk balance and, taking into account the situations listed in the Commission Delegated Regulation (EC) No 357/2014. The justification should provide explicit information as to which situation(s) it corresponds.

* 1. Conclusions on clinical aspects

Conclude on clinical aspects and carry forward open issues to the list of questions.

<Based on the presented bioequivalence study(ies) <(INVENTED) NAME> is considered bioequivalent with <REFERENCE PRODUCT>.

*OR*

<Due to the following reasons < ELABORATE ON THE REASONS > <(INVENTED) NAME> is not considered bioequivalent with <REFERENCE PRODUCT>.

If applicable; The results of study <STUDY NUMBER> with <XXmg> formulation <CAN/CAN NOT> be extrapolated to other strengths <XX mg>, according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1, section 4.1.6

In case the generic/hybrid contains a different salt, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of the active substance, include the appropriate statement:

<A summary of the literature with regard to clinical data of {medicinal product} and justifications that the different <salt><ester><ether><isomer><mixture of isomers><complex><derivative> of the active substance does not differ significantly in properties with regards to safety and efficacy of the reference product were <not>provided and are <not>accepted by the CHMP. This is <not> in accordance with the relevant guideline and additional clinical studies are <not> considered necessary.>

*A brief statement about the conclusions that can be drawn from any clinical efficacy documentation should be provided here, too.*

[Note regarding Obligation to complete post-authorisation measures:   
In a limited number of cases, data that are considered as “key” to the benefit risk balance may be requested as a condition of the MA. In case issues have been identified for inclusion in Annex II as conditions, use the following statement. Any measure identified as a condition needs to be well motivated, notably the need for a condition should be explained in the context of a positive benefit/risk balance. In particular, conditions related to post-authorisation efficacy studies should explicitly refer to situation(s) as listed in the Commission Delegated Regulation (EC) No 357/2014.]

<The CHMP considers the following measures necessary to address the issues related to pharmacology:><The (Co-)Rapporteur considers the following measures necessary to address the clinical issues:>

1. Pharmacovigilance
   1. Risk management plan

The RMP(s) of the reference/combined product(s) should be followed and cases of divergence (if any) need to be discussed and highlighted.

**Safety Specification**

If any data on Safety Specifications Parts II SI to SVII are submitted by the applicant, the rapporteur can complete this section.

The Safety Specification (Part II, SVIII) from RMP version XXX, dated dd-mm-yy is assessed below:

**Summary of the safety concerns**

[This corresponds to Module SVIII Summary of the Safety Specification].

Table SVIII.1: Summary of safety concerns

| **Summary of safety concerns** | |
| --- | --- |
| Important identified risks | <List> |
| Important potential risks | <List> |
| Missing information | <List> |

***Assessor’s comment:***

Comment on whether the applicant’s proposal is adequate based on the assessment of the provided data and in line with the reference product.

State specifically if a safety concern needs to be added, removed, or changed.

Having considered the data in the safety specification,

* <The Rapporteur agrees that the safety concerns listed by the Applicant are appropriate.>

*or*

* <The Rapporteur considers that the following issues should be addressed :>

<In line with the reference product, the Rapporteur considers that the following should also be <a> safety concern(s):>

<In line with the reference product, the Rapporteur considers that the following should not be <a> safety concern(s):>

*The issues to be addressed must be included in the List of Questions.*

* 1. Pharmacovigilance system

<The Rapporteur considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.>

<The Rapporteur, having considered the data submitted in the application was of the opinion that it was not appropriate to conclude on pharmacovigilance system at this time.><See list of questions>.

<The Rapporteur, having considered the data submitted in the application was of the opinion that a pre-authorisation pharmacovigilance inspection is required>.

Assessor’s comment

1. List of questions as proposed by the (Co-)Rapporteur
   1. Non-clinical aspects

Major objections

<None>

<Pharmacology>

<Pharmacokinetics>

<Toxicology>

Other concerns

<None>

<Pharmacology>

<Pharmacokinetics>

<Toxicology>

* 1. Clinical aspects

Major objections

<None>

<Pharmacokinetics>

<Pharmacodynamics>

<Risk management plan>

<Pharmacovigilance system>

Other concerns

<None>

<Pharmacokinetics>

<Pharmacodynamics>

<Risk management plan>

<Pharmacovigilance system>

* 1. <Orphan similarity and derogations>

Major objections

Other concerns

1. List of references