[insert only for CHMP adopted doc & add EMA header and footer]

Amsterdam, <insert full date>

<insert Doc.Ref.>

Committee for Medicinal Products for Human Use (CHMP)

Rapporteur day 80 critical assessment report

Overview and list of questions – generic/hybrid medicinal products

Or <DRAFT> CHMP day 120 list of questions

(generic/hybrid medicinal products)

<Invented name>

<Active substance>

EMEA/H/C/<xxx>

Applicant: <xxx>

[Delete this table at the time of adoption of D120 LOQ]

| CHMP Rapporteur: |  |
| --- | --- |
| <CHMP co-rapporteur:> |  |
| PRAC 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 save or 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):** |  |
| **Applicant:** |  |
| **Applied Indication(s):** |  |
| **Pharmaco-therapeutic group**  **(ATC Code):** |  |
| **Pharmaceutical form(s) and strength(s):** |  |
| **CHMP Rapporteur contact person:** | Name:  Tel:  Email: |
| **<CHMP Co-Rapporteur contact person:>** | Name:  Tel:  Email |
| **EMA Product Lead** | Name:  Tel:  Email: |
| **PRAC Rapporteur contact person:** | Name:  Tel:  Email:> |
| **CHMP Rapporteur assessors**  **(internal and external):** | **Quality:**  Name(s)  Tel:  Email:  **Non-clinical:**  Name(s)  Tel:  Email:  **Clinical:**  Name(s)  Tel:  Email: |
| **<CHMP Co-Rapporteur assessors**  **(internal and external):>** | **Quality:**  Name(s)  Tel:  Email:  **Non-clinical:**  Name(s)  Tel:  Email:  **Clinical:**  Name(s)  Tel:  Email: |
| **PRAC Rapporteur assessors**  **(internal and external):** | Name(s)  Tel:  Email:> |

Declarations

This application includes an Active Substance Master File (ASMF):

Yes

No

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 (including the Product Information document) here:

This template is aimed for generic and hybrid applications. If, apart from bioequivalence studies, other (non)-clinical data have been submitted, the template should be supplemented with relevant headings from the general templates of assessment report for non-clinical and clinical data.

List of abbreviations

1. <Rapporteur><CHMP> Recommendation

Based on the review of the data on quality, <safety> and <efficacy>, the generic/hybrid application for <product name> in the treatment of <claimed indication>,

<is considered approvable. Some points could be resolved after the marketing authorisation (see section 5. ).>

<could be approvable provided that satisfactory answers are given to the "other concerns" as detailed in the List of Questions. Failure to resolve other concerns may render the application not approvable>. <In addition, recommendations are made for conditions for marketing authorisation and product information (see section 5. ).> <However, the answers to the "other concerns" may affect the final product information and/or other conditions for the marketing authorisation.>

<is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the List of Questions (see section 5. ).>

<In addition, satisfactory answers must be given to the "other concerns" as detailed in the List of Questions.>

<The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies :>

<Deficiencies arising from concerns over the restricted part of the ASMF are mentioned in the appendix (this appendix is not supplied to the applicant). These concerns will be conveyed in confidence to the holder of the ASMF.>

* 1. Questions to be posed to additional experts
  2. Proposal for inspection
     1. GMP inspection(s)

[For pre-approval inspections to verify GMP compliance]

<A request for GMP inspection <is required><has been adopted> for the following site(s) in order to verify the GMP compliance status. The outcome of this/these inspection(s) is required for the Committee to complete its examination of the application and will be needed by Day 181.>

And/or

[For pre-approval inspections to cover product or process related issues]

<A request for GMP inspection <is required><has been adopted> for the following site(s) in order to provide further product specific information. The outcome of this/these inspection(s) is required for the Committee during its examination of the application and will be needed by Day 121.>

* + 1. GCP inspection(s)

[For routine GGP inspections]

<A request for GCP inspection <is required><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 <is required><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. <Similarity with authorised orphan medicinal products>

It is considered that <name of product> <is> <could be> <is not> similar to <name of authorised orphan medicinal products> within the meaning of Article 3 of Commission Regulation (EC) No. 847/200 <provided that satisfactory responses are given to the concerns as detailed in the List of Questions>.

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

It is considered that pursuant to Article 8 of Regulation (EC) No. 141/2000 and <Article 3 of Commission Regulation (EC) No 847/2000> the following derogation<s> laid down in Article 8.3 of the same Regulation <apply/ies> <could apply provided that satisfactory responses are given to the concerns as detailed in the List of Questions> <do/es not apply>:

<the holder of the marketing authorisation for <authorised orphan medicinal product> is unable to supply sufficient quantities of the medicinal product>

<the applicant could establish in the application that the medicinal product, although similar to <authorised orphan medicinal product>, is safer, more effective or otherwise clinically superior (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) for the same therapeutic indication>

<the holder of the marketing authorisation for <authorised orphan medicinal product> has given his consent to the applicant.>

1. Executive summary

GENERAL GUIDANCE

Give a one-page summary stating the main aspects of the Quality, Non-Clinical and Clinical aspects of the dossier and the assessors’ conclusions and any important deficiencies in the dossier. If everything is standard and normal, just say so. Keep this executive summary focussed and simple.

* 1. Problem statement

[Rationale for the product: epidemiology, main features of the disease and current therapy.]

* 1. About the product
  2. The development programme/compliance with CHMP guidance/scientific advice
  3. General comments on compliance with GMP, GLP, GCP
  4. Type of application and other comments on the submitted dossier
     1. Legal basis
* <Article 10(1)> of Directive 2001/83/EC, as amended – relating to applications for generic medicinal product.
* <Article 10(3)> of Directive 2001/83/EC, as amended– relating to applications for hybrid medicinal product.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than <6><8><10> years in the EEA:

* Product name, strength, pharmaceutical form:
* Marketing authorisation holder:
* Date of authorisation: (dd-mm-yyyy)
* Marketing authorisation granted by:
  + < Union >
  + <Member State (EEA) : {identify Member State}

- National procedure

- MRP/DCP>

* Marketing authorisation number:

Medicinal product authorised in the Union /Members State where the application is made or European reference medicinal product:

* Product name, strength, pharmaceutical form:
* Marketing authorisation holder:
* Date of authorisation: (dd-mm-yyyy)
* Marketing authorisation granted by:
  + < Union >
  + <Member State (EEA) : {identify Member State}

- National procedure

- MRP/DCP>

* Marketing authorisation number:

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

* Product name, strength, pharmaceutical form:
* Marketing authorisation holder:
* Date of authorisation: (dd-mm-yyyy)
* Marketing authorisation granted by:
  + < Union>
  + <Member State (EEA) : {identify Member State}
    1. - National procedure
    2. - MRP/DCP>
* Marketing authorisation number(s):
* Bioavailability study number(s):

<Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, < (1)> < (2) point(s) (a) (b) (c) (d) (e)> - Extensions of marketing authorisations>

* + 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>.

* + 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> or < the holder of the marketing authorisation for the original orphan medicinal product is unable to supply sufficient quantities of the medicinal product> or <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. Scientific overview and discussion

The structure of this AR is in accordance with the Day 80 Overview and will be updated at the different stages of the CHMP review (Day 150/180/CHMP AR/EPAR) so as to constitute a self-standing document. See also the Day 80 Overview Guidance.

It should therefore be sufficiently detailed to eventually be used for the CHMP (Withdrawal) AR and (W)EPAR and give sufficient justifications for the LoQ/LoOI as appropriate.

Tables and graphs to display results are encouraged.

In the case of additional pack-sizes which contain more units than the pack sizes of the reference product, this should be reflected in the overview. Furthermore, it should be confirmed that all pack sizes are consistent with the dosage regimen and duration of use.

* 1. Quality aspects

|  |
| --- |
| **The purpose of the Overview Quality AR is to support the scientific opinion and recommendation issued by the CHMP. In order to achieve that it should present in a brief, summarised way those details necessary to understand what is in the application for the MAA and sufficiently address the conclusions of the evaluation. The focus should be on the significant and noteworthy findings and aspects from the critical assessments on Quality as detailed and captured in the Quality AR.**  **A self-standing and focused elaboration is expected in order to allow the reader comprehensive understanding of the relevant findings affecting the benefit-risk assessment. The Overview should be a brief summary of the quality AR and should focus on the main conclusions and discussion/interpretation of the results giving the grounds for the benefit-risk assessment, the CHMP recommendations and/or the questions, especially the Major Objections (MO),raised to the applicant should be included in a concise and succinct manner. The level of detail would depend on the complexity of the product and the quality of the dossier.**  **For each section, consider addressing the following points:**  **1) Identify the most important findings and deficiencies described above (do not repeat results). Summarise evidence for each conclusion.**  **2) State if the data submitted fulfil the requirements.**  **3) Describe the major issues raised and to what extent they have been/should be addressed.**  **4) Highlight important issues that need to be/have been discussed during CHMP (or QWP/ QWP Core Team) meetings during the assessment of the medicinal product.**  **The structure of the document is in accordance with the LoQ AR, Day 150/180 AR and EPAR structure and should thus be updated at the different stages of the CHMP review. The Overview is not intended as a history of the assessment and instead it should rather reflect the status at each milestone of the evaluation procedure. Nevertheless in this context it may be useful and indeed more meaningful to reflect how the most controversial points of each application have been addressed and resolved, for example resolution of MOs, or how the AS /FP specification or the control strategy has evolved/changed during the evaluation.**  **This is particularly important in view of the need for a CHMP AR at the time of the opinion or a possible withdrawal or access to document requests.**  **Please note that for simplicity, not all CTD headings are reproduced in the report structure that follows, only the ‘main’ headings. Assessors may add more, or less, depending upon the complexity of the product; please also refer to the CTD guidance text for the applicant. In addition, note also that the CTD terms ‘Drug Substance’ and ‘Drug Product’ are synonymous with the EU legislative terms ‘Active Substance’ and ‘Finished Product’ respectively. The terms active substance and finished product are preferred to be used in the overview.**  **The template should be seen as an acceptable “baseline”. It includes some proposed standard sentences that could be used for simple generics where no controversial issue was identified during the evaluation. It is not intended for complex generics or hybrid applications but it can be also be used if relevant. However, it is not exhaustive. More information will need to be included depending on the specificities of each product. Any deviations from Guidelines should also be reflected together with a short discussion on why they were found to be acceptable, or not.**  **There should be a link between the recommendations (REC) for future development (CHMP AR 2.2.6) and the scientific discussion. Wherever such a REC is proposed, details can be given in 3.2.4 Discussion and conclusions section.**  **In case quality issues have been identified for inclusion in Annex II as conditions, they need to be well motivated in the CHMP AR, and should be explained in the context of a positive benefit-risk balance.**  **Refer to this link <http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000037.jsp> for more information regarding Annex II conditions and recommendations.**  **The aim of this guidance document is to cover chemical products. It is also not intended to be used as a checklist but rather as assistance to the assessor to critically distil the quality AR into a succinct and comprehensive summary.**  **KEY:**  **AS: active substance**  **FP: finished product** |

* + 1. Introduction

The following text may be used:

<The finished product is presented as <pharmaceutical form(s)> containing <strength(s)> of <INN> as active substance.

Other ingredients are: (include the list of excipients as described in section 6.1)

The product is available in <primary packaging as described in section 6.5 of the SmPC>.

Mention Medical Devices, if it is part of the presentation of the medicinal product.

* + 1. Active Substance
       1. General Information

Include nomenclature: At least one sentence to mention the name of the AS. Confirm whether the name is INN, Common Name, etc.

Provide the structure, MW and chemical formula of the AS.

The chemical name of <INN/Common name> is <chemical IUPAC name(s)> corresponding to the molecular formula <CxHyNzOn>. It has a relative molecular mass of <xxx.x> g/mol and the <following structure:>

Insert active substance structure

**Figure 1: Active substance structure**

The chemical structure of <active substance> was elucidated by a combination of… The solid state properties of the active substance were measured by…

Summary of proof of structure confirmation – should not be too long for an ‘established’ substance. Add physicochemical characterisation as relevant (GVS, DSC, XRPD etc.)

The <active substance> is a <physical state> <solid-state properties>, <hygroscopicity>, <solubility>.

General Properties that are relevant to the product development (e.g. oxygen, air or light stability) or to the performance of the product in the clinic (e.g., solubility, polymorphism, isomers, particle size etc.) should be mentioned.

<INN> exhibits stereoisomerism due to the presence of <number> chiral centres. *<*Enantiomeric purity is controlled routinely by chiral HPLC/specific optical rotation.> *Or* <active substance> has a non - chiral molecular structure>.

Refer to the sources of stereoisomerism e.g. starting materials. Mention how it is controlled e.g. SM specs or intermediate specs or reaction conditions.

Polymorphism has <not> been observed for <active substance>.

Mention how many polymorphs have been identified (in literature or by experimental data), which of those are relevant/possible via the proposed manufacturing process. Mention how polymorphism is controlled. In case of polymorphism, briefly describe if it is relevant to the performance of the product.

In case a CEP is provided, the following sentence may be added:

As there is a monograph of <active substance> in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for <active substance> which has been provided within the current Marketing Authorisation Application.

* + - 1. Manufacture, process controls and characterisation

Mention the name and number of sources/suppliers (manufacturers, ASMFs) of the active substance.

The active substance is manufactured by .

In case a CEP is provided, add the following sentence:

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

In case of ASMF procedure is used, use the following sentence in addition to the information above:

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Reflect the discussion re the SMs if applicable e.g. if MO were raised and how these have been resolved (by redefinition or by justification).

<active substance> is synthesized in <number> main steps using <commercially available> well defined starting materials with acceptable specification<s>.

Insert synthetic scheme(s)

**Scheme 1: Active substance manufacturing process**

Very brief description of synthesis if important to quality of finished product. Mention key steps with impact on API purity and physical properties, e.g. steps generating key impurities, those with CPPs, milling for inhaled/poorly soluble APIs. Chiral drugs – mention origin of stereochemical control. Highlight any re-processing/ re-processing/ recovery (e.g. from mother liquors or filtrates) of solvents, reactants, intermediates or the active substance, etc.

The process flowchart or reaction scheme may be included if needed. When relevant mention key steps with impact on AS purity and physical properties, e.g. steps generating key /genotoxic impurities, those with CPPs, milling for inhaled/poorly soluble ASs. For chiral drugs mention the origin of stereochemical control.

If the AS is supplied as a sterile material, discuss the adequacy of the process validation studies.

Critical information regarding the control of materials should be included in a concise manner, where relevant.

For polymorphism, state the specific polymorphic form manufactured and whether it has been shown stable upon storage (may refer to stability data).

Discuss if the process is sufficiently described and the overall control strategy (including in process controls, testing of starting material, monitoring of process parameters etc) and the risk mitigation measures are adequate to control the process leading to an AS of intended and consistent quality. Summarize deficiencies if found.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

In case the manufacturing process for the active substance has been changed during development consider the following as appropriate:

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program.

<Changes introduced have been presented in sufficient detail and have been justified.>

<Several> <important> changes have been introduced during the development of the manufacturing process, including a change in the.…………………. It has been demonstrated that the change(s) did not have a significant impact on the quality of the product.>

<The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.>

Summarize the key aspects/stages of the manufacturing process development that are essential in providing reassurance with regard to the AS quality e.g. important process changes through clinical/pharmaceutical development.

Summarise relevant studies related to the control strategy (e.g. how critical process parameters have been identified) and mention if QbD elements have been used (risk assessment, DoE, prior knowledge, etc.); provide a short summary of those and confirm if the approach is acceptable. Briefly discuss how acceptable ranges were established and if the data provided in support of the ranges is acceptable.

*If a Design Space (DS) is claimed, describe which steps of the synthesis it covers and at which scale the DS was developed. State if it is acceptable and explain whether verification of the DS is needed at commercial scale.*

If proven acceptable ranges (PARs) are proposed, mention the steps of the manufacturing process for which they have been established.

If a verification protocol has been proposed, explain briefly what aspect it relates to and if it can be accepted.

State if holding times are proposed and discuss whether they are acceptable.

*Mention the container closure system for the active substance and compliance with relevant requirements.*

<The active substance is packaged in *<material>* which complies with EC 10/2011 as amended.>

* + - 1. Specification (s)

Discuss whether the proposed AS specifications limits, tests and methods are acceptable. If there are several sources of active substances (e.g. several ASMFHs) include the specification used by the manufacturer of the finished product. A table of the current specifications should be included.

The active substance specification shown in **Table 1** includes tests for <mention the latest specification and the tests methods in brackets, for example: appearance, identity (IR, HPLC), assay (HPLC), impurities (HPLC), residual solvents (GC), water content (KF), heavy metals (ICP-MS), and residue on ignition (Ph. Eur.)>

**Table 1: Active substance specification(s)**

Insert spec table

Include a copy of the final agreed specifications table.

Discuss the acceptability of the proposed acceptance criteria, mention briefly how they have been established/ justified and if this is in accordance with the relevant guidelines as appropriate. Discuss if the acceptance criteria of stated impurities have been justified based on general ICH thresholds where applicable or qualified in non-clinical and clinical studies or clinically justified by other means as appropriate.

Reference and discussion re specific impurities or other materials (catalysts, residual solvents etc) is possible if specific issues need to be reflected in the AR.

<Impurities present at higher than the qualification threshold were qualified by toxicological, mutagenic and clinical studies and appropriate specifications have been set.>

Omission of tests at the AS level due to testing at intermediate stages should be discussed and it should be stated if it has been accepted.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for <assay> <and> <impurities> testing has been presented.

Batch analysis data (n=<number of batches> and scale) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Refer to the CEP, if there is one. Additional tests considered to be necessary, apart from the Ph.Eur. monograph, should be mentioned.

The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph. In case of additional parameters: Additional specifications have been set for <additional parameters>. All additional methods have been adequately validated and described according to ICH Q2.

State clearly whether the AS is going to be released by real time release testing (RTRT). If RTRT is proposed, comment on the appropriateness of controls of the critical process parameters and critical materials attributes that would justify RTRT.

Mention if the use of more than one sources of the active substance affects the specifications and the acceptability of this.

* + - 1. Stability

Stability data from <number, scale> batches of active substance from the <proposed> manufacturer(s) stored <in the intended commercial package><in a container closure system representative of that intended for the market> <if not describe the package> for up to <number> months under long term conditions (xx ºC / xx% RH, i.e. .25 ºC / 60% RH) and for up to <number> months under accelerated conditions (xx ºC / xx% RH i.e., 40 ºC / 75% RH) according to the ICH guidelines were provided. <Photostability testing following the ICH guideline Q1B was performed on <number> batches>. <Results on stress conditions <describe the stress conditions> were also provide on <number> batches.>

The following parameters were tested*: <* list of parameters which change during storage and likely to influence the quality of the active substance>. < The analytical methods used were the same as for release and were stability indicating (if not mention, which additional methods were used).>

Discuss the stability results and if they showed any significant changes or trends. Discuss if the observed physical and chemical changes are likely to have a significant effect on efficacy and safety of the product when stored for the proposed shelf life under recommended conditions. Summarise the stability results in a brief yet informative manner. e.g. <All tested parameters were within the specifications.>, <Degradation products increased under accelerated conditions but remained within the specification.>

If more than one supplier is proposed, discuss whether stability data are representative of all suppliers and whether there are any differences in stability. Discuss any relevant findings identified during the stability studies. Discuss any out of specifications results and mention the conclusions in this respect

Use the following statement with respect to ongoing stability programs: “Any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA”.

Any supportive data should be discussed briefly (e.g. from previous versions of the synthesis or laboratory scale batches).

If a CEP is provided and contains a re-test period, make only reference to the CEP.

The stability results indicate that the active substance manufactured by the proposed supplier(s) is sufficiently stable. The stability results justify the proposed retest period of x months <storage conditions> in the proposed container.

* + 1. Finished Medicinal Product
       1. Description of the product and Pharmaceutical Development

Describe the finished product (pharmaceutical form, strengths and differentiation thereof, physical appearance, devices) and solvent (if included in the product package) as described in section 3 of the SmPC.

The composition of the finished product is presented in Table 2.

**Table 2: Composition of Finished product**

A table detailing the qualitative and quantitative composition of the finished product should be included. The function of each ingredient should be indicated.

Indicate any overage or overfill.

For standard generics the following sentence can be used:

The finished product has been developed to be a generic equivalent to the reference medicinal product *<Name of the reference medicinal product>*. Consequently, the objective was to prepare a *<pharmaceutical form>* being essentially similar to the reference medicinal product.

Briefly describe the rationale behind formulation development and highlight if there are special features (e.g. whether QbD elements have been used).

State if different strengths come from the same blend, comment on proportionality of composition vis-à-vis biowaivers.

Discuss whether the chosen formulation adequately accommodates the active substance’s physicochemical properties (stability, incompatibilities, solubility, route of administration etc.). Discuss the differences (if any) and their relevance between the intended commercial formulation and those used in the reference medicinal product if different.

Only excipients which are critical for the development of the finished product and novel excipients may be mentioned here with their function.

If all the excipients are not critical, please use the following standard sentence:

<All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.>

Compatibility studies between the active substance and excipients may be briefly described.

Mention differences to qualitative and quantitative composition of the product (excipients) with the reference medicinal product, impurity profiles, etc. and discuss their relevance.

Discuss key aspects of development (non-exhaustive list):

* How the QTPP leads to / dictates the final formulation/pharmaceutical form / manufacturing process. present key steps of formulation and manufacturing development and the rationale driving it e.g.
  + hydrolysis/photosensitive/degradation prone AS -> how formulation development addressed that.
  + heat/hydrolysis/photo/degradation sensitive AS - how manufacturing process development has dealt with them. (e.g. aseptic filling vs terminal sterilisation, impact on storage conditions choice of container closure system.
  + water insoluble AS -> polymorph control for the AS but also during manufacture and stability.
* Other characteristics :
  + preservative system,
  + stabilisers (e.g. cobicistat, vitamin D).
  + sterilisation method justified (refer to media fill studies(?) if applicable (for aseptic filling)).
  + polymorph conversion during manufacture and storage
  + Mention any overage or overfill
* If specific pharmaceutical form:
  + modified release->briefly mention the release mechanism.
  + liposomes, micelles-> consider discussing concentration, size, stability, fate(?) etc.
  + novel excipients.
  + injectable formulations-> refer to sterility (terminal or aseptic, reasons for choice), leachable/extractable studies, compatibility studies (with solvents/diluents and or administering devices(catheters).
  + inhaled products -> discuss delivered/ inhaled dose, particle/ droplet size etc.
* Manufacturing process development-> elaborate if non-standard.

If medical device is involved discuss (at least) in the development. (e.g. inhalers but also measuring devices).

In addition, for generic medicinal products with bioequivalence studies:

Compare the formulation to the formulation of the reference product.

For generics where the formulation is different from the originator/reference product, state the differences and discuss in the light of comparable safety issues, e.g. special warning statements for certain excipients, and the effect of certain excipients on the performance of the product in comparison to the reference. Make a comment as to whether these formulation differences are considered to be significant (or not, in the case of a positive opinion). Mention the comparative dissolution study, especially for waiver.

If there was no BE study and a biowaiver was granted discuss the quality aspects of the biowaiver. Same applies for strength biowaivers. Discuss how the in vitro studies have been conducted and what conclusions they led to.

Biowaiver of strengths <include the strengths> has been applied. The product meets the general requirements according to Guideline on Investigation on Bioequivalence (CHMP/EWP/QWP/1401/98 Rev 01). Based on the information provided the biowaiver can be accepted.

Relate the characteristics of the active substance and the formulation to bioavailability where relevant.

If a dissolution method was developed, please, describe it briefly, and discuss how the discriminatory power has been demonstrated.

<The discriminatory power of the dissolution method has been demonstrated.>

Comment on the selection /design of the manufacturing process, taking into account the product particularities (e.g. dry/wet granulation, products that cannot be terminally sterilised by heat treatment).

Comment on the selection of the sterilisation process e.g. whether terminal sterilisation is performed, if possible and applicable.

Highlight the main aspects of manufacturing process development and summarise relevant studies (e.g. how critical process parameters have been identified).

If QbD elements have been used in the pharmaceutical development/ manufacturing development / process design (risk assessment, prior knowledge, DoE to support Design Space, etc.); provide a short summary of those and confirm if the approach is acceptable.

Discuss any site transfers during pharmaceutical development.

Discuss the differences (if any) and their relevance, between the intended commercial process and those used for the production of clinical batches.

If the medicinal product includes components which are classified as medical devices (e.g. needles, catheters, etc.), discuss if they are CE-marked and whether they comply with the relevant medical devices legislation. If the device is incorporated with the medicinal product, comment on its suitability in relation to the clinical performance of the product (e.g. dosing accuracy). State if conformance with the essential requirements of Annex I of Regulation (EU) 2017/745 has been demonstrated.

Briefly, mention extractables/leachable studies performed if relevant and state if they are acceptable.

Discuss the choice and suitability of the packaging material and its compliance with the relevant requirements as outlined in the AR. Indicate if the container closure system is/ is not suitable for use based on development studies, stability studies, ISO criteria, etc.

*Describe the container closure system and discuss its compliance with relevant requirements (Ph.Eur., ISO standards), as appropriate*

The primary packaging is <describe as stated in the SmPC>. <The material complies with Ph.Eur. and EC requirements>. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

* + - 1. Manufacture of the product and process controls

Mention the number and names of the manufacturers and in which countries the manufacturers are located.

Provide a brief description of the manufacturing process and mention whether the process is standard or non-standard. Comment on the level of detail in the description of the manufacturing process provided by the applicant.

The manufacturing process consists of <number> main steps: <list the steps>. The process is considered to be a <non> standard manufacturing process.

Insert FP flow diagram

Scheme 2: Finished product manufacturing process

State if holding times are proposed and discuss whether bulk packaging and holding times are acceptable.

Highlight process control of critical steps only and discuss whether they are adequately controlled. The assignment of the critical steps should be discussed. Consider elaborating on specialised / pivotal methods.

Unless already described in the pharmaceutical section above, discuss the adequacy of the overall control strategy, including whether process parameters and in-process controls are adequately set to control the process leading to consistent quality.

Briefly discuss how the acceptable process ranges were established and if data provided in support of the ranges is acceptable.

Mention the process validation / verification protocols and studies as applicable and discuss if they are adequate e.g. type of studies, scale, models used and cover the proposed commercial process. The acceptability of protocols should be indicated.

If non-standard process, discuss the adequacy of the validation data and any justification related to process validation e.g. in relation to the manufacturer’s experience with the specific process.

<Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this <type of manufacturing process> <pharmaceutical form>. >

* + - 1. Product specification (s)

Specification summary, test methodology

The finished product release and shelf life specifications shown in Table 3 include appropriate tests for this kind of dosage form <include the latest specification parameters at release with the tests in brackets>.

**Table 3: Finished product release and shelf specifications**

Discuss whether the proposed release and shelf life specifications, and related analytical tests are acceptable. A table of the proposed commercial specifications should be included.

Discuss the acceptability of the proposed acceptance criteria, mention briefly how they have been established and comment on whether these are sufficiently justified. Discussion on specific impurities or other attributes may be included if any issues need to be reflected.

Summarise changes introduced during the MAA procedure (e.g. tightening of specifications) and mention if there are any post-authorisation measures (recommendations) to amend / review specifications when further manufacturing experience has been gained.

*Reference to and discussion regarding elemental impurities. The following standard sentence may be used: <*The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach.> *Plus, as applicable:* <Batch analysis data on <n> batches using a validated <ICP-MS> method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE.> <Based on the risk assessment <and the presented batch data> it can be concluded that <it is not necessary to include any elemental impurity controls>> ***or***<the following elemental impurities <*list*> are included> in the finished product specification. The information on the control of elemental impurities is satisfactory.>

*Reflect the discussion on the potential presence of nitrosamines and the performed risk assessment*. *The following standard text may be used if applicable:* <A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the “Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products” (EMA/409815/2020) and the “European Medicines Regulatory Network approach for the implementation of the CHMP Opinion pursuant to Article 5(3) of Regulation (EC) Nº 726/2004 for nitrosamine impurities in human medicines (EMA/425645/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.>

Mention the proposed analytical procedures if not included in the specification table and comment on their suitability. Elaborate more on specialised / pivotal methods e.g. potency assays, dissolution (discriminatory power) etc.

Discuss whether the proposed procedures have been satisfactorily validated and if they are adequate to control the finished product on a routine basis, i.e. as a release test.

Comment on the adequacy of information regarding the reference standards or materials.

Omission of testing or any deviation from the guidelines should be discussed and justify why it has been accepted.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for <assay> <and> <impurities> testing has been presented.

In case a QbD approach is followed in support of analytical method flexibility, mention the method for which it is requested and if it is acceptable.

State if further data are required leading to a post-authorisation measure (Recommendation) (e.g. additional/complementary validation studies).

State clearly whether the finished product is going to be released to the market by real time release testing (RTRT). If RTRT is proposed, comment on the appropriateness of controls of the critical process parameters and critical materials attributes that would justify RTRT.

Discuss the adequacy of batch analysis results, the batch size of the tested batches and batch-to-batch consistency.

Batch analysis results are provided for <number+ scale> batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

* + - 1. Stability of the product

State clearly the claimed shelf-life/ in-use period and storage conditions as per the SmPC.

Include background information to understand the basis for the approved storage conditions, including in-use storage conditions, where relevant.

Confirm whether stability studies / conditions were performed according to ICH guidelines and if not why they have been accepted. Comment on the scale of batches and their representativeness of the commercial product.

Stability data from <number, scale> batches of finished product stored for up to <number> months under long term conditions (xx ºC / xx% RH , i.e. 25 ºC / 60% RH) and for up to <number> months under accelerated conditions ( xx ºC / xx% RH , i.e. 40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of <medicinal product> are <identical> <representative><different> to those proposed for marketing and were packed in the primary packaging proposed for marketing.

If more than one AS supplier is proposed, discuss whether stability data are representative of all suppliers and whether there are any differences in stability.

Samples were tested for <include the shelf life specifications if different from the release specifications>. The analytical procedures used are stability indicating. *If the parameters tested are the same as for release used the following sentence* <The analytical methods used were the same as for release and were stability indicating.>

*Briefly discuss the stability results e.g. no trends, or increase of X impurity etc. for normal stability , in-use and photostability etc.* *Results should confirm* <…no significant changes have been observed.> *or alternatively that:*

<…observed physical and chemical changes were small, and not likely to have a significant effect on efficacy and safety of the product when used according to the directions in the SmPC.>

Discuss any out of specifications results and mention the conclusions in this respect. Discuss any relevant findings identified during the stability studies, especially discuss findings that led to shelf-life restrictions or storage precautions.

In case bracketing/matrixing is used, discuss the acceptability.

For oral solid products: mention stability studies outside the primary container, only if such data/information has been submitted (should not be requested unless a need is anticipated.

Discuss the stability results and if they showed significant changes or trends, and conclude on whether the observed physical and chemical changes are (not) likely to have a significant effect on efficacy and safety of the product when used according to the directions in the SmPC. If any out of specifications results were observed, mention the conclusions in this respect.

Stability in refrigerated/freezer conditions and any information on temperature cycling testing should be reflected, especially for critical formulations.

Discuss results from in-use stability studies if relevant and mention if an in-use stability text is needed or can be excluded in the SmPC.

Discuss results from photostability and stress studies.

Discuss the stability recommendations as indicated in the SmPC after opening (in-use), reconstitution, dilution, mixing with food etc., or compatibility with administration devices and the performance of the Ph.Eur. preservative efficacy test as appropriate.

Based on available stability data, the proposed shelf-life of X months and <storage conditions> as stated in the SmPC (section 6.3) are acceptable.

State if further stability data are required as part of a post-approval measure(Recommendation), e.g. additional in-use stability studies, full scale data following introduction of a lately introduced additional manufacturing facility while comparability and primary stability data already available.

* + - 1. <Post approval change management protocol(s)>

If a post approval change management protocol (PACMP) has been proposed explain briefly what aspect it relates to and if it can be accepted.

* + - 1. Adventitious agents

Highlight any TSE aspects of starting materials, reagents, excipients, adjuvants, active substance and confirm the adequacy of the information.

For example, add as relevant:

<It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.>

<Gelatine obtained from bovine sources is used in the product. Valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided. >

< No excipients derived from animal or human origin have been used.>

* + 1. Discussion and conclusions on chemical, pharmaceutical and biological aspects

**Please also refer to section 8 of the D80 Quality AR guidance document.**

Mention only the significant points of discussion as described in sections 3.1.2 and 3.1.3 to allow the reader comprehensive access to the relevant findings thus enabling adequate benefit risk assessment. Take caution that this should not be a reiteration of the section 3.2.3. Mention those aspects from the active substance and finished product that are related, e.g. specifications of drug substance are too wide which result in too wide limits for finished product.

In relation to the Quality aspects impacting the benefit-risk balance, indicate if there is any quality aspect either in the active substance or in the finished product which could lead to impact on the benefit-risk Balance. Consider particularly the following aspects:

- Is the control strategy sufficient to guarantee consistent/ satisfactory quality/performance of the product?

- Is there sufficient stability data to ensure safe use?

- Are the batches used in clinical trials representative with regard to the commercial product to guarantee that the latter will be the same as the clinical batches?

Mention briefly the Major Objections during the assessment and how they have been resolved.

At the time of a positive Opinion:

- For standard non-contentious products a standard wording may be used along the following lines:

“…Information on development, manufacture and control of the active substance and finished product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.”

- In case quality 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 in the CHMP AR, notably the need for a condition should be explained in the context of a positive benefit-risk balance:

“The CHMP has identified the following measures necessary to address the identified quality developments issues that may have a potential impact on the safe and effective use of the medicinal product:”

Plus, in case of recommendations:

“At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the benefit-risk balance of the product.”

Alternatively, in the case of a **negative quality report**, contributing to a **negative CHMP Opinion**, the **main** quality problems need to be highlighted here and repeated in the final benefit-risk statement, later in the report (section 5).

* + 1. **Conclusions on the chemical, pharmaceutical and biological aspects**

The following "standard" wording could be considered:

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. <Data has been presented to give reassurance on viral/TSE safety>.

In case quality 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 in the CHMP AR, notably the need for a condition should be explained in the context of a positive benefit/risk balance:

<The CHMP has identified the following measures necessary to address the identified quality developments issues that may have a potential impact on the safe and effective use of the medicinal product:>

It is needed to justify the measures when the quality could impact in the safety and efficacy and why the benefit/risk remains positive

* + 1. **Recommendation(s) for future quality development**

<In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:>

**There should be a link between the recommendations listed in this section and the scientific discussion. It should be clear to the reader why CHMP gives these recommendations.**

* 1. Non clinical aspects

**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. <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.>

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

<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 have been submitted e.g. 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 SmPC. In such case a new non- clinical assessment has to be performed.

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.

* + 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
    4. Ecotoxicity/environmental risk assessment

Section to be completed for all generic/hybrid medicinal products.

<No Environmental Risk Assessment studies were 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.>

OR

1. 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. Discussion on non-clinical aspects
    2. Conclusion on non-clinical aspects
  1. Clinical aspects

This template is aimed for generic and hybrid applications. If, apart from bioequivalence studies, other clinical data have been submitted, please fill in the following sections, as appropriate.

* + 1. Exemption

• Tabular overview of clinical studies

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

* + 1. Clinical pharmacology
       1. Pharmacokinetics

Study <Number>: <Title>

Methods

* Study design

* Test and reference products
* Population(s) studied

* Analytical methods

* Pharmacokinetic Variables
* Statistical methods

Results

* <Safety data>

Include this section ONLY if no separate section “Clinical safety” will be included (see below). Provide a very brief summary of the adverse events observed in the bioequivalence study. No conclusion in terms of comparison between test and reference should be made based on these data.

* + - 1. Pharmacokinetic Conclusion
      2. Pharmacodynamics

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

* + 1. Discussion on clinical pharmacology

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 were 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 one 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.

* + 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
* 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. Discussion on clinical efficacy
    2. <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

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

* + 1. Discussion on clinical safety
    2. Conclusions on clinical aspects

<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 was <not> provided and was <not> accepted by the CHMP. This is <not> in accordance with the relevant guideline and additional clinical studies were <not> considered necessary.>

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

Whenever there is an impact on the Benefit / Risk, please elaborate here on the clinical issue (s) that led to this conclusion:

[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.]

* 1. <Risk management plan>

[**At D80** the CHMP rapporteur should assess the safety specification within the RMP and fill in the sections below. The CHMP Co-Rapporteur should only flag safety findings which may be relevant for the RMP.

**Prior to circulation of the Draft D120 LOQ**, the additional sections assessed by the PRAC Rapp (pharmacovigilance plan, risk minimisation measures, annexes) should be added by the CHMP rapporteur once the PRAC Rappporteur AR has been finalised.

The RMP(s) should be aligned with that of the reference/combined product(s) and any divergence needs to be highlighted and justified.

* + 1. Safety Specification
       1. Summary of safety concerns

[**To be filled in by the CHMP Rapporteur at D80 and updated in subsequent D120** document considering comments from the CHMP Co-Rapporteur (if any), the PRAC rapporteur and Member States.

Specifically address the need to modify the Safety specification and the summary of safety concerns.

If there are no safety concerns state “None.”]

The applicant proposed the following summary of safety concerns in the RMP:

Table SVIII.1: Summary of safety concerns

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

* + 1. Discussion on safety specification

[**Complete this section at D80:** Specifically address the need to modify the Safety specification based on the reference product.]

**At D120, this section should be updated** considering comments from the CHMP Co-Rapporteur, the PRAC rapporteur and Member States]

* + 1. Conclusions on the safety specification

[**Complete this section at D80 and update it prior to circulation of the Draft D120 LOQ**]

Having considered the data in the safety specification,

* <It is agreed that the safety concerns listed by the Applicant are appropriate.>

*or*

* <It is considered that the following issues should be addressed :>

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

<In line with the reference product, it is considered 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 plan

**[Leave blank at D80. This section is assessed by the PRAC rapporteur in their D94 PRAC Rap. AR]**

**[Prior to circulation of the Draft D120 LOQ,** copy here the tables from the PRAC Rapporteur RMP AR “Pharmacovigilance plan” or from section III.3 Summary Table of additional Pharmacovigilance activities of the RMP of the applicant.]

Comment on whether routine pharmacovigilance is sufficient or whether additional activities are warranted. Comment on whether proposed activity(ies) is(are) appropriate and in line with the reference product or if due to the differences between the generic product and the reference product, a post-authorisation safety study will be necessary to collect further data on the safety concern [specify the safety concern].]

<Please refer to the D94 PRAC Rapp RMP AR.>

* + 1. Risk minimisation measures

**[Leave blank at D80. This section is assessed by the PRAC rapporteur**]

**Prior to circulation of the Draft D120 LOQ** copy here the table from the latest PRAC Rapporteur RMP AR “Risk minimisation measures or from section V.3 Summary of risk minimisation measures.”

Comment on whether risk minimisation activities as proposed by the applicant are sufficient and in line with the reference product or whether additional risk minimisation measures are needed.

If there are no risk minimisation measures state “None.”]

<Please refer to the D94 PRAC Rapp RMP AR.>

* + 1. Conclusion on the RMP

[**Leave blank at D80.** **Complete this section prior to circulation of the Draft D120 LOQ**]

[Choose one of the following options, based on the latest assessment report version.

<The RMP is acceptable><No new risks have been identified for the generic product that are not recognised for the reference product and there are no outstanding issues.>

*or*

<The RMP is acceptable with minor revisions required for the next update.>

*or*

<The RMP could be acceptable provided an updated RMP and satisfactory responses to the <list of questions below is submitted.>

*or*

<The RMP is not acceptable.>

* 1. Pharmacovigilance
     1. Pharmacovigilance system

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

<Having considered the data submitted in the application, it is not appropriate to conclude on pharmacovigilance system at this time.><See list of questions>.

<Having considered the data submitted in the application, a pre-authorisation pharmacovigilance inspection is required>.

* + 1. *Periodic Safety Update Reports submission requirements*

[**Leave blank at D80**. This section is assessed by the PRAC rapporteur in its D94 PRAC Rapp AR]

[This section should be completed by the PRAC Rapporteur prior to D120. For generic/hybrid applications, current EURD list entry is usually followed.]

[**Option 1:** If the substance is not included in the EURD list, the new EURD list entry will be based on the IBD or EBD; request the applicant to indicate whether they wish to align the EBD to IBD with an additional question in the list of question and use the following statement:]

<The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did <not> request alignment of the PSUR cycle with the international birth date (IBD). <The IBD is {DD.MM.YYYY.}>. The new EURD list entry will therefore use the {EBD} {IBD} to determine the forthcoming Data Lock Points.>

For the LOQ: <The applicant should indicate if they wish to align the PSUR cycle with the international birth date (IBD)>.

[**Option 2:** If the substance is already included in the EURD list, evaluate whether the relevant entry is valid for the MAA. If the relevant entry could not be valid for the MAA (e.g. a specific entry for a particular indication/pharmaceutical form/legal basis is needed), the PRAC Rapporteur should verify if a separate entry is needed]

[In case the already existing entry is valid for the MAA, use the following statement:]

<The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.>

[In case a separate entry is needed, liaise with the applicant to clarify whether they wish to align the EBD to IBD and use the following statement]

<Based on {provide scientific reason}, the CHMP is of the opinion that a separate entry in the EURD list for {invented name} is needed, as it cannot follow the already existing entry for {active substance}. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did <not> request the alignment of the new PSUR cycle with the international birth date (IBD). {The IBD is DD.MM.YYYY.} The new EURD list entry will therefore use the {EBD} {IBD} to determine the forthcoming Data Lock Points.>

For the LOQ:

<The applicant should indicate if they wish to align the PSUR cycle with the international birth date (IBD)>.

[In case the already existing entry needs to be amended on the basis of the data submitted with the MAA, complete the following statement, providing the rationale for such amendment.]

<Based on {provide scientific reason}, the CHMP is of the opinion that the already existing entry in the EURD list for {active substance} needs to be amended as follows: the PSUR cycle for the medicinal product should follow a <half-yearly> <yearly> cycle. The next data lock point will be {date}. >

1. Benefit/risk assessment

**For generic application (Art 10.1),** consider the below text and modify as appropriate:

<This application concerns a generic version of [active substance] [pharmaceutical form]. The reference product [invented name] is indicated for [therapeutic indication]. No nonclinical studies have been provided for this application but an adequate summary of the available non-clinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant’s clinical overview on these clinical aspects based on information from published literature is considered sufficient.

The bioequivalence study forms the pivotal basis with a [*design summary*]. The study design is considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. [*Comment on appropriateness of parallel design, studies in fed status, investigation of metabolites, etc*]. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied are adequate.

The test formulation of *[applied product]* met the protocol-defined criteria for bioequivalence when compared with the *[reference product]*. The point estimates and their 90% confidence intervals for the parameters AUC0-t, AUC0-∞, and Cmax were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated.

When different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of the active substance of the reference medicinal product are used, additional information providing proof that their safety and/or efficacy profile is not different from that of the reference medicinal product should be submitted and the overall conclusion should be addressed here.

<This application contains a different <salt><ester><ether><isomer><mixture of isomers><complex><derivative> of the active substance. A summary of the literature with regard to non-clinical and 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><but> was <not>accepted by the <Rapporteur> <CHMP>. This is <not> in accordance with the relevant guideline and additional <non> clinical studies were <not> considered necessary.>

A benefit/risk ratio comparable to the reference product can therefore <not> be concluded.>

**For hybrid application (Art 10.3),** consider the below text and modify as appropriate:

<This application concerns a hybrid version of [active substance] [pharmaceutical form]. The reference product [invented name] is indicated for [therapeutic indication]. Nonclinical studies have been provided for this application and considered sufficient. From a clinical perspective, this application does <not> contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant’s clinical overview on these clinical aspects based on information <from published literature> was considered sufficient.

The bioequivalence study forms the pivotal basis with a [design summary]. The study design is considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. [Comment on appropriateness of parallel design, studies in fed status, investigation of metabolites, etc]. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of [applied product] met the protocol-defined criteria for bioequivalence when compared with the [reference product]. The point estimates and their 90% confidence intervals for the parameters AUC0-t, AUC0-∞, and Cmax were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated.

When different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of the active substance of the reference medicinal product are used, additional information providing proof that their safety and/or efficacy profile is different from that of the reference medicinal product should be submitted and the overall conclusion should be addressed here.

<This application contains a different <salt><ester><ether><isomer><mixture of isomers><complex><derivative> of the active substance and additional non clinical studies in accordance with the relevant guideline were submitted and were <not> considered sufficient.

A benefit/risk ratio comparable to the reference product can therefore <not> be concluded.>

<Having considered the data submitted in the application and available on the chosen reference medicinal product, no additional risk minimisation activities are required beyond those included in the product information.>

OR

<Having considered the data submitted in the application and available on the chosen reference medicinal product, the following risk minimisation activities are necessary for the safe and effective use of the medicinal product:>

[Then list activities and key elements/text as appropriate if educational material is a risk minimisation activity]

<The application contains inadequate < quality > <non clinical> <and> <clinical data> <and> the bioequivalence has not been shown>. The aspects that are inadequately demonstrated are outlined in the List of Questions: >

* 1. Conclusions

The overall benefit /risk balance of <name of product> <is positive subject to the conditions stated in the Recommendations’ section ‘><is negative.>

1. <Proposed> <CHMP> <List of questions>

(Make cross-references from the actual question to what is stated in the scientific discussion. Limit the “other concerns” to what is needed to know.)

* 1. Quality aspects
     1. Major objections

Drug substance *(related to additional data provided by applicant only)*

Drug substance *(applicant’s part as provided by ASMF holder)*

Note: In case the ASMF procedure is used the following should be stated in case potential serious risks to public health are being raised on the restricted part of the ASMF:

“For potential serious risks to public health on the restricted part of the ASMF see separate Appendix on the ASMF”

Note: When applicable:

“For Other concerns on the restricted part of the ASMF see separate Appendix on the ASM

**Drug product**

* + 1. Other concerns

Drug s**ubstance** (related to additional data provided by applicant only)

Drug substance (applicant’s part as provided by ASMF holder)

Note: When applicable:

“For Other concerns on the restricted part of the ASMF see separate Appendix on the ASMF”

Drug product

* 1. Non clinical aspects
     1. Major objections

Pharmacology

Pharmacokinetics

Toxicology

* + 1. Other concerns

Pharmacology

Pharmacokinetics

Toxicology

* 1. Clinical aspects
     1. Major objections

Pharmacokinetics

Pharmacodynamics

Clinical efficacy

Clinical safety

* + 1. Other concerns

Pharmacokinetics

Pharmacodynamics

Clinical efficacy

Clinical safety

* 1. Risk management plan
     1. Major objections
     2. Other concerns

Public Summary of the RMP Regarding the public summary of the RMP, the Applicant should update the Part VI “Summary of activities in the risk management plan by medicinal product”, in line with the issues raised in other parts of the RMP.

* 1. Pharmacovigilance
     1. Major objections
     2. Other concerns
  2. <Orphan similarity and derogations>
     1. Major objections
     2. Other concerns

1. Recommended conditions for marketing authorisation and product information in case of a positive opinion

In case of major objections, inclusion of the following sentence may be considered:

<In view of the major objections it is premature to recommend any conditions for marketing authorisation and to propose changes in the product information (SmPC, Annex II, labelling, PL). The assessment of the user consultation or of the justification for not having them and any above risk minimisation questions should however be addressed.>

* 1. Conditions for the marketing authorisation

[For example legal status, conditional marketing authorisation, exceptional circumstances/specific obligations and other post-authorisation measures. Details of the risk management plan.

The (co)rapporteurs should review and comment on the draft Annex II, as proposed by the applicant, in the Product Information document.

* 1. Proposed list of post-authorisation measures\*

[This table should be reserved to include post authorisation measures that are part of the marketing authorisation, such as specific obligations, Annex II conditions, or any additional studies that have arisen based on the assessment of the data]

The proposed post-authorisation measures are subject to assessment of responses to the List of Questions:

| **Post-authorisation measure(s)** | **Motivation** |
| --- | --- |
| Proposed post-authorisation measure 1 with proposed classification: | Motivation/Background information on measure, including due date: |
| 1. |  |
| Proposed post-authorisation measure 2 with proposed classification: | Motivation/Background information on measure, including due date: |
| 2. |  |
| Proposed post-authorisation measure 3 with proposed classification: | Motivation/Background information on measure, including due date: |
| 3. |  |
| Proposed post-authorisation measure X with proposed classification: | Motivation/Background information on measure, including due date: |
| X. |  |

\* Classification: category 1= Annex II D condition; category 2= Annex II E specific obligations; category 3 = All other studies reflected only in the RMP (PASS)

Proposed list of recommendations:

Recommendations pertain to quality, non-clinical (e.g. ERA, PK/PD, PAES if not key to the B/R).

| **Description of post-authorisation measure(s)** |
| --- |
|  |
|  |

* 1. Other conditions

*[Please state in this section all additional risk minimisation measures.]*

* 1. Summary of product characteristics (SmPC)

[The rapporteur should only comment in sections specific to the generic/hybrid application(s)]

* 1. Labelling
  2. Package leaflet (PL)

User consultation

*[for guidance please see D80AR Overview guidance]*

Conclusion from the checklist for the review of user consultation

<Quick Response (QR) code>

<The review of the QR code request submitted by the MAH is presented in a separate attachment to this report (checklist available for download here: [Quick Response (QR) code](http://www.ema.europa.eu/docs/en_GB/document_library/Template_or_form/2016/01/WC500199877.doc" \t "_blank)). >

1. Appendices (as appropriate)
   1. <Co-><Rapporteurs><CHMP> questions on the ASM (Active Substance Manufacturer) restricted part of the ASMF

[NOTE that this annex should not be sent to the MA Applicant but only to the holder of the ASMF.]

* 1. AR on similarity dated < >
  2. AR on derogations dated < >

1. QRD checklist for the review of user testing results

[Disclaimer: This guidance has been developed to provide practical information on how to evaluate user testing reports which are based on the readability testing method as described in the Annex to the EC Readability Guideline. This does not exclude the submission and evaluation of user testing reports based on other methods than the one outlined above, for which specific assessment guidance may be issued once experience has been gained.]

Useful links: More detailed practical guidance can be found in the following documents:

EC Readability Guideline:

<https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-2/c/2009_01_12_readability_guideline_final_en.pdf>

“Operational procedure on Handling of “Consultation with target patient groups” on Package Leaflets (PL) for Centrally Authorised Products for Human Use [https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/operational-procedure-handling-consultation-target-patient-groups-package-leaflets-centrally\_en.pdf](http://www.emea.europa.eu/htms/human/qrd/qrdplt/27737805en.pdf)

“Consultation with Target Patient Groups-meeting the requirements of Article 59(3) without the need for a full test-Recommendations for Bridging” <https://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/Consulation_PatientsGroups/CMDh_100_2007_clean.pdf>

“Position paper on user testing of package leaflets” <https://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/Consulation_PatientsGroups/CMDh_234_2011_Rev01_2016_12_clean.pdf>

**PRODUCT INFORMATION**

| Name of the medicinal product: |  |
| --- | --- |
| Name and address of the applicant: |  |
| Name of company which has performed the user testing: |  |
| Type of Marketing Authorisation Application: |  |
| Active substance: |  |
| Pharmaco-therapeutic group  (ATC Code): |  |
| Therapeutic indication(s): |  |
| Orphan designation | yes  no |
| CHMP Rapporteur/CoRapporteur |  |

- Full user testing report provided  yes no

- Focus test report provided  yes no

- Bridging form provided[[1]](#footnote-2)  yes no

*[In case full user testing or focus test reports have been provided, please use the checklist for review of user testing results included in this document.]*

- In case bridging form1 has been provided, please perform the assessment in the bridging form and state the overall conclusion/recommendations below:

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

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*[In case no user testing report or bridging form has been provided, a justification should be submitted by the applicant.]*

- Is the justification for bridging acceptable?  yes  no

- Is the justification for not submitting a report acceptable?  yes  no

*[The following are examples of what are not considered valid justifications for not performing user testing:*

*Administration in a hospital setting only,*

*Orphan indication, therefore difficult to recruit participants from this population,*

*- Administration by a healthcare professional only,*

*- Compliance with the QRD templates,*

*- Long established use of the product.*

Reasons *[assessor’s views on acceptability or not of the justification for not submitting user testing report or bridging form]*

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1. Technical assessment

**1.1 Recruitment**

* Is the interviewed population acceptable?  yes  no

no information

Comments/further details:

VIII.4.1 Guidance regarding Recruitment

The following points should be taken into consideration when assessing recruitment methods:

* Is the recruitment method well defined? Is it clear that serious thought was given to the composition of the test group? (e.g. in terms of variables such as sex, age, education, previous job titles (in case of retirement, change of employment), job description and professional experience (e.g. vocational training, complete qualifications, use of information technology) in order to assess their level of education, experience with the medicinal product, existing knowledge of the complaint, access to information technologies, etc.). Is a detailed description of the subjects’ profiles available?- How has the test group been recruited? Are they new users or patients, parents or carers?
* Is a listing of any respondents who volunteered previously in user testing and how often they have done so available?
* Is it clear how many people were involved in the test/test rounds?
* Is that number sufficient? (The PL should be tested in minimum 2 rounds of 10 participants each)

**1.2 Questionnaire**

* Is the number of questions \_\_\_\_\_\_\_ sufficient?  yes  no  no information
* Questions cover significant (safety) issues for the PL concerned?  yes  no

no information

Comments/further details:

VIII.4.2 Guidance regarding Questionnaire

The following points should be taken into consideration when assessing the questionnaire:

* Have the key messages for safe use been identified by the applicant? Is it clear how the questions were selected /drafted? The critical safety issues should be discussed prior to preparing the questionnaire.
* Do the questions cover the key messages and the following areas?

=>General impressions of package leaflet;

=>“Diagnostic” part of PL (i.e. questions aiming to test whether the participants were able to find specific information quickly and easily in each section of the PL and to verify if they were able to understand this information correctly; the questionnaire should primarily concentrate on safety and correct use of the medicinal product and understanding of the participant to assure safe use –it must be ensured that key safety messages have been addressed);

=>Aspects such as design and layout of PL.

* Is the number of questions sufficient? (too few or too many – e.g. 12- 15)
* Do the questions address “wording” aspects? Can respondents easily understand the text they are reading?
* Is the number of questions sufficient? (too few or too many – e.g. 12- 15)
* Do the questions address “wording” aspects? Can respondents easily understand the text they are reading?
* Do the questions provide open or pre-defined answers? Respondents should not be provided with ready-made answers which would increase the possibility of positive results. They should instead answer in their own words in order to check if they understand the information correctly. Questions should be open, should be ordered randomly to see how patients use the PL and should not be leading (however, it is good practice to start with an easy question to ease the participant). Questions that require self-assessment (example: in your opinion, is paragraph X clear?) should not be used. Questions that require a long list of answers to be given (example: “what are the adverse events of this medicinal product?”) should also not be used.

**1.3 Time aspects**

* Is the time given to answer acceptable?  yes  no  no information
* Is the length of interview acceptable?  yes  no

no information

Comments/further details:

Guidance regarding Time aspects

The following points should be taken into consideration when assessing the time aspects:

* Is it clear how long the test lasted?
* Was the time given for respondents to read and answer the questions adequate? How long did the interview last? [The test should be designed in a way to last no more than 45 minutes, to avoid tiring participants]
* Is it clear at which point would a question be considered “not answered”? E.g. simply because the respondent took too much time to find and / or understand it? (It should not take more than 2 minutes to find the answer).

**1.4 Procedural aspects**

* Rounds of testing including pilot \_\_\_\_\_\_\_  yes  no  no information

Comments/further details:

Guidance regarding Procedural aspects

The following points should be taken into consideration when assessing the procedural aspects:

Is the test based on different testing rounds? (a minimum of two test rounds, each involving 10 participants, is required: As this is an iterative process more rounds may be required in order to satisfy the success criteria; a pilot test (including 2 to 3 persons) could precede to assure the questionnaire is understood and major gaps are precluded. The PL after changes should then be tested on 20 participants in total. However, one single testing round may also be considered sufficient and acceptable on a case-by-case basis)

A satisfactory test outcome for the method outlined above is when 90% of literate adults are able to find the information requested within the PL, of whom 90% can show they understand it, i.e. each and every question must be answered correctly by at least 81% of the participants.

In practice, it means to have 16 out of 20 participants able to find the information and answer each question correctly and act appropriately. However, it need not be the same 16 participants in each case. The success criteria will need to be achieved with each question. Results cannot be aggregated.

* Does it makes use of modification phases in-between the testing rounds in order to maximise readability?
* Do interviewers use scenarios or live demonstrations (e.g. in order to increase the efficiency of the test, if appropriate.

**1.5 Interview aspects**

* Was the interview conducted in well structured/organised manner?  yes  no

no information

Comments/further details:

Guidance regarding Interview aspects

The following points should be taken into consideration when assessing the interview aspects:

* Is the time given to the participants to read the leaflet before the interview starts clearly stated? (It should not be more than 15 minutes).
* Are there clear instructions for the test instructor(s)? (e.g. instructions on how to get more information from the consumers test, whether or not help should be given, etc.)
* Do interviewers let respondents show where information on the medicinal product can be found in the leaflet?
* Do they ask respondents to give their answer in their own words and not to rely on memory?
* Is there an internal Standard Operative Procedure (SOP) upon which the whole exercise was based?

2. Evaluation of responses

**2.1 Evaluation system**

* Is the qualitative evaluation of responses acceptable?  yes  no

no information

* Does the evaluation methodology satisfy the minimum prerequisites?  yes  no

no information

Comments/further details:

Guidance regarding Evaluation system

The following points should be taken into consideration when assessing the evaluation system:

* Is the assessment based on a check list covering the following 3 basic areas:

Whether the respondent was able:

- To find the information (e.g. can a respondent easily find the information on dosage?)

- To understand the information (e.g. can a respondent say in his/her own words what the proper dosage and the instructions for use are?)

- To use the information (e.g. “imagine you are in situation X and Y happens, what must you do?”)

* Does the report identify difficulties (if any) in finding or understanding certain questions? If so, are these difficulties analysed? And, more importantly, are they addressed in the PL?
* If the company recorded the body language and behaviour of the participant, it should be described how it will influence the assessment/ results of the user testing.

**2.2 Question rating system**

* Is the quantitative evaluation of responses acceptable?  yes  no

no information

Comments/further details:

Guidance regarding Questions rating system

The following points should be taken into consideration when assessing the questions rating system:

* How are answers evaluated? (e.g. 1= no answer, 2=wrong answer, 3=incomplete answer, 4=ambiguous answer, 5=complete and correct answer)

3. Data processing

* Are data well recorded and documented?  yes  no

no information

Comments/further details:

Guidance regarding Data processing

The following points should be taken into consideration when assessing the data processing:

* Is it clear how the data are recorded? e.g. videotape, audiotape or in writing.
* Is it clear how long the data are kept for after the end of the study?
* Is the way in which they are recorded satisfactory?
* Have the data been processed satisfactorily? (e.g., is it clear how verbal assessments have been converted into graded answers?)
* Has the assessor been provided with the patient leaflets used during (different rounds of) testing?
* Are the revisions in the PL explained/justified? Is it also clear which comment from the participants were ignored and why?

4. Quality aspects

**4.1 Evaluation of diagnostic questions**

* Does the methodology follow Readability guideline Annex?  yes  no

no information

* Overall, each and every question meets criterion of 81% correct answers (e.g. 16 out of 20 participants) yes  no

no information

Comments/further details:

**4.2 Evaluation of layout and design**

* Follows general design principles of Readability guideline  yes  no
* Language includes patient friendly descriptions  yes  no
* Layout navigable  yes  no
* Use of diagrams acceptable  yes  no

Comments/further details:

Guidance regarding Quality aspects

The following points should be taken into consideration when assessing the quality aspects:

* Is the report complete?
* Does the report clearly distinguish between quantitative and qualitative results?
* Is the medicinal product and the company concerned clearly indicated?
* Based on EC guidelines, are “diagnostic” questions (see 1.2) scoring satisfactorily?
* Do respondents find the layout and design of the package leaflet satisfactory?

Special focus should be given to the following elements:

* Writing style (simple language, short sentences, use of bullets)
* Type face (font size, italics/underlining, lower/upper case)
* Layout (spacing, white space, contrast, left justified, columns)
* Headings (consistent location, stand out)
* Use of colour (present, adequate contrast)
* Pictograms should be subject to user testing as it is well known that these can confuse patients.
* Do respondents encounter difficulties in locating and using correctly (if appropriate) the information provided in the PL?
* Is it clear whether general or specific comments on design and layout have been implemented? If not, has a justification been provided?

5. Diagnostic quality/evaluation

* Have any weaknesses of the PL been identified?  yes  no
* Have these weaknesses been addressed in the appropriate way?  yes  no

Comments/further details:

Guidance regarding Diagnostic quality/evaluation

The following points should be taken into consideration when assessing diagnostic quality/evaluation:

* Are the results (as far as possible) related to actual passages of text?
* Is an attempt made to explain that readers’ problems arose because of certain characteristics of those passages (e.g. something was difficult to find because of a badly chosen heading; or a passage could not be understood because of a double negative; or specific information could not be applied properly because certain terms were unclear)?
* Was a second round revision carried out?
* Have weaknesses of the first round been clearly identified and addressed in the appropriate way? (e.g. questions that scored low led to modifications on the PL => introduction of stylistic changes to improve readability or removal of redundant and confusing information)
* Is it clear which passages have been revised and how and on the grounds of what observations in the first round?
* Is it also clear what observations were ignored in making the revision and why?
* Have modifications been tested and proved to improve readability?
* Is it clear what changes were made in between the different rounds (pilot, 1st and 2nd)? (e.g. summary of PL changes highlighted before and after? Has a new PL with track changes been included in the report reflecting changes between different rounds?)
* Have mock-ups used for each round been submitted? Is the final version the one which has been submitted with the application to be assessed?

6. Conclusions

* Have the main objectives of the user testing been achieved?  yes  no
* Is the conclusion of applicant accurate? yes  no
* Overall impression of methodology  positive  negative
* Overall impressions of leaflet structure  positive  negative

**CONCLUSION/OVERVIEW**

Guidance regarding conclusion

*A general view on the user testing performed and on the overall readability /quality of the PL should be provided here [to be used in the Day 80, Day 150 or Day 180 assessment report as appropriate and the CHMP assessment report – the complete evaluation report of the user testing results should only be included as an Annex of the Day 80 or Day 150 assessment report, as appropriate]*

*The following points should be taken into consideration when drafting the conclusions:*

*Objectives:*

1. To ensure the final PL reflects the results of testing with patients to make sure it meets their needs and can enable the patient to use the medicinal product safely and effectively. The overall quality of the PL should be the absolute focus rather than confirming a successful 81%+ for each and every question.
2. To assess the readability of the PL
3. To identify problems regarding comprehensibility and usefulness of information
4. To describe possible changes in the leaflet in order to improve the readability of the leaflet
5. To ensure that all comments, especially the ones related to design, lay-out, general impression (free text comments), have been taken into account.

* Does the report make it clear on what test results specific conclusions are based?
* Do the conclusions match the results or, given the actual results, is too favourable a picture painted?
* Are the conclusions clear, concise and well organised?

Have the recommendations and conclusions also been incorporated in any revision of the text?

1. [QRD form for submission and assessment of user testing bridging proposals [EMA/355722/2014]](http://www.ema.europa.eu/docs/en_GB/document_library/Template_or_form/2014/12/WC500179551.doc) [↑](#footnote-ref-2)