Template 3

Instructions and template for comments and peer review of the initial assessment reports from (Co) Rapporteurs

The overall aim of the Peer Review is to **contribute to the quality assurance** of the LoQ intended for the applicant by reviewing the proposed questions in conjunction with the scientific reasoning made by the (Co) Rapporteurs in their initial assessment reports. The peer review may encompass the whole or selected parts of the Q/E/S assessment as decided by the CHMP at the time of the assignments.

The peer review should adhere to this template and both Rapporteur’s and Co Rapporteur’s assessment reports should be peer reviewed if appropriate according to the objectives of the peer review. The peer reviewers will systematically address the following 2 main aspects when filling in the relevant parts of the template:

1. The extent to which the **scientific argumentation** in the (Co) rapporteurs’ assessment reports supports the proposed questions in the LoQ.

2. The **consistenc**y between issues raised in the Day 120 LoQ and the CHMP guidelines/Scientific Advice and issues raised in the assessment of products within the same class/same indication.

However in order to be able to address those two main aspects, particularly in the context of different views expressed by the two rapporteurs and/or by other CHMP members, the peer reviewer also needs to confirm or not that the initial assessment reports describe different topics in sufficient detail to allow secondary assessment (in practice this means that the (Co) Rapporteur’s assessment reports should fulfil criteria set out in template and guidance documents adopted by the CHMP. -

In this context, the topics listed in the addendum to this annex could be used as a checklist/guidance to which topics in the AR are principally important for the peer review).

The peer review/QA exercise is based on the different modules – Quality, Non-Clinical, Clinical and Overview/LoQ of the (Co)Rapporteurs’ initial assessment reports which should be sufficiently readable, detailed (and self-explanatory) to allow the peer reviewer to critically assess pivotal data without having to read the original application dossier. It is recognised however that in order to address some specific issues that may arise during their assessment, the Peer Reviewers shall have access to the overview/expert report (module 2 of the application). Exceptionally, selected parts from other modules may be necessary and can be requested at the peer reviewer’s discretion. As a consequence of the peer review, proposals to **modify and improve on the LoQ** could be made by the peer reviewer to the (Co) Rapporteur but it may also be that parts of the assessment reports, the conclusions/benefit risk assessment and especially the overview, or the SPC could be considered for modification.

Peer review comments are most useful when they are both critical and constructive, proposing specific changes to the assessment and the LoQ!

Anyway the **Rapporteurs remain responsible** for the content of the different parts of the assessment reports and the proposed “Overview and LoQ” and will consider what changes to be considered for inclusion in the documents.

Peer Reviewers Comments at Day 100

1. This document is sent by:

Name of Peer Reviewer <name>

Email address:<email address>

Experts / Assessors: <name>, <email address>

Date of Review: <date>

1. These Peer Review comments concerns:

Rapporteur's Assessment Report

Co-Rapporteur's Assessment Report

**[[1]](#footnote-1)🕇**Rapporteur:

**🕇**Co-Rapporteur: <name>, <email address>

**🕇**EMA EPL: <name>, <email address>

**🕇**EMA PM: <name>, <email address>

and are raised on the following parts of the Assessment Report:

Quality

Non-Clinical

Clinical

RMP

Draft LoQ

Product: <Invented Name> <INN>

1. Indication (4.1) - <proposal by the applicant>:

<indication>

Please try to be both critical and constructive: proposing specific changes

1. General comments

1. Specific Comments

Quality Aspects

Non-Clinical Aspects

Clinical Aspects

Risk Management Plan

1. List of Questions

Quality Aspects

Non-Clinical Aspects

Clinical Aspects

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Risk Management Plan

Peer Reviewer’s Checklist for topics to be considered. – This list has been accumulated based on the most frequent objections raised during the initial CHMP review (Eur J Clin Pharmacol (2002) 58:573-580 and the CONSORT (Consolidated Standards of Reporting Trials) statement. CONSORT includes a checklist that includes items, based on evidence, that need to be addressed in the report. See further <http://www.consort-statement.org/> or click for example item II:2 under “Clinical” below.

Peer Review Quality

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| 1. Synthesis of the active substance |
| 2. Pharmaceutical development of the finished product. |
| 3.Bibiological/Biotech development (e.g. genetics, fermentation, purification), manufacture and control. |
| 4.Batch consistency (e.g. variable manufacturing process). |
| 5. Transmissible agents (e.g. viruses. |
| 6. Active substance (e.g. Biologicals, Biotech). |
| 7. Manufacture and quality control for the active substance (e.g. control methodology, method validation etc) |
| 8. Finished product or its formulation (e.g. control methodology, method validation, specification limits etc.) |
| 9. Stability of the active substance |
| 10. The stability of the finished product. |

**Peer Review Non Clinical**

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| ***I. Pharmacodynamics*** |
| 1. Primary pharmacodynamics. |
| 2. Study design or data to support claimed mechanism or claimed receptor selectivity |
| 3. Secondary pharmacodynamics. |
| 4 Safety pharmacology. |
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| ***II. Pharmacokinetics*** |
| 1. Study design and the number of animals. |
| 2.if applicable: Pharmacokinetic differences to humans with implications for the toxicity studies (e.g. if a major human metabolite is not found in animals) |
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| ***III Toxicology*** |
| 1. Study design of the single-dose and repeat toxicity studies. |
| 2. Safety margins in single-dose and repeat toxicity studies. |
| 3.Target organs in single-dose and repeat toxicity studies (being relevant to humans). |
| 4. Reversibility in acute and repeat toxicity studies. |
| 5. Immunotoxicity. |
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| ***IV Genotoxicity*** |
| 1. Genotoxicity *in vitro.* |
| 2. Genotoxicity *in vivo.* |
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| ***V Carcinogenicity*** |
| 1. Study design. |
| 2. Safety margins. |
| 3. if applicable: target organs relevant for humans? |
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| ***VI Reproductive Toxicity*** |
| 1 Safety margins. |
| 2. if applicable: findings relevant to humans. |
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| ***VII Environmental toxicity*** |
| 1. Adequacy of studies |

**Peer Review Clinical Efficacy**

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| ***I Clinical Pharmacology*** |
| 1. Justification for the dose/dose regimen. |
| 2. ADME |
| 3. Interaction studies. |
| 4. Studies in special populations (e.g. liver, renal, pregnancy, females,). |
| 5. Pharmacodynamics. |
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| ***II General issues on study design*** |
| 1. Controlled trials described as randomised. |
| 2. M[ethod used to generate the random allocation sequence, including details of any restrictions](http://www.consort-statement.org/examples9.htm) (e.g., blocking, stratification). |
| 3. [Generation of the allocation sequence, enrolment of participants, and assignment of participants to their groups](http://www.consort-statement.org/examples10.htm). |
| 4. Group allocation described as concealed. |
| 5. Justification for the choice of control group (active or placebo). |
| 6 Justification for other study design than RCT. |
| 7. Method for a blinded/unbiased outcome assessment described. |
| 8. Handling of missing data. |
| 9. Inclusion and exclusion criteria. |
| 10. Primary and secondary endpoints. |
| 11. Determination of [sample size](http://www.consort-statement.org/examples7a.htm) |
| 12. if applicable: [explanation of any interim analyses and stopping rules](http://www.consort-statement.org/examples7b.htm). |
| 13. S[tatistical methods used to compare groups for primary outcome(s)](http://www.consort-statement.org/examples12a.htm) and [methods for additional analyses,](http://www.consort-statement.org/examples12b.htm) such as subgroup analyses and adjusted analyses. |
| 14. Proposed Hypothesis |
| 15 Prospectively defined primary or secondary analysis. |
| 16. Description of the analysis population (intention to treat or per protocol). |
| 17. Appropriateness of the analysis population (e.g. ITT vs. per-protocol). |
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| ***III. Analysis/robustness of pivotal data/selection of submitted studies*** |
| 1.Description of the flow of participants. |
| 2 Information on the d[ates defining the periods of recruitment and follow-up.](http://www.consort-statement.org/examples14.htm) |
| 3 B[aseline demographic and clinical characteristics of each group given](http://www.consort-statement.org/examples15.htm). |
| 4. Statistically significant results for the primary endpoint. |
| 5. [For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision](http://www.consort-statement.org/examples17.htm) (e.g., 95% confidence interval). |
| 6. M[ultiplicity](http://www.consort-statement.org/examples18.htm) (by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those prespecified and those exploratory). |
| 7. Protocol deviations and reasons. |
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| ***IV. Issues of validity*** |
| 1. Appropriateness of patient population studied (including aspects on children, elderly, females). |
| 2. Study population in accordance with the claimed indication. |
| 3. Recruitment according to plan (or too few patients enrolled). |
| 4. Appropriateness of duration of treatment in the trials(s). |
| 5. Appropriateness of long-term follow-up data. |
| 6. Major protocol violations or other GCP issues. |
| 7. Product’s role in therapy/ its clinical usefulness (particularly for diagnostics). |
| 8. Marginal/no clinically relevant efficacy (including duration of effect). |
| 9. Inconsistent data on clinical efficacy. |

**Clinical Safety**

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| 1. Increased mortality. |
| 2 Other serious AE. |
| 3. Quality of the safety database. |
| 4. Size of the safety database. |
| 5. Long -term safety data. |
| 6. Severe or lethal clinical interactions. |
| 7. Dose/dose regimen relating to clinical safety (e.g. in renal and hepatic impairment). |
| 8. Specific interaction studies relating to clinical safety. |
| 9. Neutralising antibodies |
| 10 Possible reasons for safety concerns such as mechanistic studies. |

1. [↑](#footnote-ref-1)