Guidance document on the content of the <Co-> Rapporteur day 80 critical assessment report
Overview and list of questions

<Invented name>

<(Active substance)>

EMEA/H/C/<xxx>

Applicant:

<table>
<thead>
<tr>
<th>Rapporteur:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-rapporteur:</td>
<td></td>
</tr>
<tr>
<td>EPL:</td>
<td></td>
</tr>
<tr>
<td>PM:</td>
<td></td>
</tr>
<tr>
<td>Start of the procedure:</td>
<td></td>
</tr>
<tr>
<td>Date of this report:</td>
<td></td>
</tr>
<tr>
<td>Deadline for comments:</td>
<td></td>
</tr>
</tbody>
</table>
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### Administrative information

| Invented name of the medicinal product: | Name:  
| INN (or common name) of the active substance(s): | Tel:  
| Applicant: | Fax:  
| Applied Indication(s): | Email:  
| Pharmaco-therapeutic group (ATC Code): |  
| Pharmaceutical form(s) and strength(s): |  
| Rapporteur contact person: | Name:  
| Co-Rapporteur contact person: | Tel:  
| EMA Product Lead: | Fax:  
| Procedure Manager: | Email:  
| Names of the Rapporteur assessors (internal and external): | Quality:  
| | Name(s) | Tel:  
| | Fax:  
| | Email:  
| | Non-clinical:  
| | Name(s) | Tel:  
| | Fax:  
| | Email:  
| | Clinical:  
| | Name(s) | Tel:  
| | Fax:  
| | Email:  
| Names of the Co-Rapporteur assessors (internal and external): | Quality:  
| | Name(s) | Tel:  
| | Fax:  
| | Email:  
| | Non-clinical:  
| | Name(s) | Tel:  
| | Fax:  
| | Email:  
| | Clinical:  
<p>| | Name(s) |</p>
<table>
<thead>
<tr>
<th>Tel:</th>
<th>Fax:</th>
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<tbody>
<tr>
<td>Email:</td>
<td></td>
</tr>
</tbody>
</table>

<In accordance with Article 6(3) of Regulation (EC) No 726/2004, I the (Co) Rapporteur hereby declare that I have completed my assessment report in less than 80 days>. | Date |
| | Signature |
List of abbreviations
1. Recommendation

Based on the review of the data on quality, safety and efficacy, the Rapporteur considers that the application for <product name>, <an orphan medicinal product> in the treatment of <claimed indication>, <could be approvable provided that satisfactory responses are given to the preliminary list of questions (Section VI)> <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 preliminary list of questions (Section VI)>

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

Indicate how this recommendation is made with regard to the Conditional Approval/Exceptional circumstances opinion, as appropriate.

Proposal for questions to be posed to additional experts

Identify the need for additional expert involvement (e.g. SAG, or pharmacovigilance expertise to for example review specific safety concerns or to assess the appropriateness and feasibility of draft protocols in the Pharmacovigilance) and the questions to be posed (e.g. need for pharmacovigilance plan?)

Indicate if an Opinion is proposed to be requested from the PDCO related to aspects of the paediatric development.

Special expertise in relation with novel emerging therapies (e.g. cellular, tissue products, gene therapy).

Proposal for inspection

State the need for an inspection (GMP, GLP, GCP).

GMP inspection(s)

[For routine GMP inspections]

<A request for GMP inspection 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 triggered GMP inspections]

<A request for GMP inspection 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.>

GCP inspection(s)

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

And/or

[For triggered GCP inspections]

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

New active Substance status

Based on the review of the data the Rapporteur considers that the active substance contained in the medicinal product contained in the medicinal product...

could be qualified as a new active substance in itself in comparison to the known isomer/mixture of isomers/complex derivative/salt of {INN (salt) approved} previously authorised in the European Union as {name of the medicinal product approved} as it differs significantly in properties with regard to safety and efficacy from the previously authorised substance.

is not to be qualified as a new active substance in itself in comparison to the known isomer/mixture of isomers/complex derivative/salt of {INN (salt) approved} previously authorised in the European Union as {name of the medicinal product approved} as it does not differ significantly in properties with regard to safety and efficacy from the previously authorised substance. The concerns identified, which preclude the recommendation are detailed in the List of Questions.

2. Executive summary

GENERAL GUIDANCE

For each main section of the assessment report for modules 4 and 5, the report should describe the data submitted.

For each type of study, after distinguishing between main and supportive data, it should be assessed whether the main data consist of all the particulars and documents of non-clinical or clinical study reports ("original data"), bibliographical references, a combination of the two, or if data are absent.

The data submitted should be assessed based on the legal basis of the application, other legal/regulatory data requirements, applicable guidelines and other scientific criteria.

The types of studies addressed within each section should include all indents as listed in Annex I of Directive 2001/83, as amended.

These legislative requirements are reflected in the template headings (and CTD).
When available data deviate from legislative requirements:

Where the data submitted deviate from the requirements, the acceptability of any justifications should be assessed. In particular, absence of any data for non-clinical/clinical test or trials, or use of bibliographic references substituting in part or completely original data for main studies must be justified.

Examples of justifications and assessment of the justifications are provided in the following table:

<table>
<thead>
<tr>
<th>Justification</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific derogations foreseen in the legislation, with particular reference to Annex I of Directive 2001/83/EC, as amended</td>
<td>Mention specific derogations and confirm the reasons why the application fulfils the conditions for applying them.</td>
</tr>
<tr>
<td>Specific derogations foreseen in guidelines, with particular reference to ICH/CHMP or EC guidelines</td>
<td>Mention guidelines and specific derogations, and give reasons why the application fulfils the conditions for applying them.</td>
</tr>
<tr>
<td>Due to the extent of scientific knowledge the conduct of certain clinical trials is considered unethical(^1), or the conduct of certain animal tests is considered to lead to unnecessary use of animals(^3) (for instance, due to extensive clinical experience certain toxicological tests are considered unnecessary)</td>
<td>Discuss what evidence is the basis for the scientific knowledge, the relevance and reliability of such evidence, and assess the validity of any extrapolation. Given that evidence, assess whether repeating certain trials/tests (or conducting additional tests) would extend scientific knowledge essential for benefit/risk assessment and provision of adequate information to patients and prescribers</td>
</tr>
</tbody>
</table>


**<Claim for 1 extra-year data exclusivity (Articles 10(5) - and 74(a) of Directive 2001/83/EC, as amended)>**

This refers to “a new indication for a well-established substance” (article 10(5)) and “change of classification of a medicinal product” (article 74(a). Separate reports are also requested here (see Appendix)

**<Chemical generics>**

Note that for generic applications (chemicals) a special template for the Day 80 AR has been developed.
<Biosimilarity>

In the particular case of a “bio-comparability exercise”, the development strategy chosen by the company should be described, justified and assessed in view of the relevant guidelines.

<Significance of paediatric studies>

The assessment of significance of paediatric studies is a transitional measure and is only needed in situation where a PIP containing only studies completed before 26 January 2007 AND/OR studies initiated before this date but completed after. In this case only the studies which were initiated before this date and completed after should be assessed for their significance.

<Conformity with agreed paediatric investigation plan>

This applies only in case the Rapporteur denies conformity with the agreed PIP due to unexpected aspects not obvious at time of the compliance check performed by the PDCO (e.g. inspection finding, discrepancy in the number of patients, etc.).

2.1. Problem statement

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

2.2. About the product

Mode of action.

Pharmacological classification.

Claimed indication and recommendation for use (including a possible risk management strategy) and posology.

Special pharmaceutical aspects, if any, e.g. novel delivery system, gene therapy etc.

2.3. The development programme/compliance with CHMP guidance/scientific advice

Introduce and comment the clinical development programme in view of the proposed indication and posology.

State if, and when Scientific Advice / Protocol Assistance has been given, describe the issues and indicate whether the advice was followed by the applicant.
Indicate if the applicant followed relevant CHMP guidance and if any deviations have been adequately justified.

Indicate whether a Paediatric Investigation Plan (with or without deferral) or a product-specific waiver has been agreed with the PDCO, or whether a class waiver applies. Briefly summarise the conditions and principal requirements of the paediatric investigation plan with regard to clinical aspects, if applicable, and state the relevant key information about the current status of the clinical studies (i.e. completed, studies ongoing, etc).

Indicate availability and need for development in other special populations such as the elderly, male/female and ethnic minorities. State the number and characteristics of healthy volunteers/patients/males/females included in the studies, as appropriate. The table used in section III.1 of the clinical assessment may be used (from CTD table 2.7.3.1).

**2.4. General comments on compliance with GMP, GLP, GCP**

Elaborate as appropriate in concordance with points made in the critical assessment modules.

A specific comment should be made as to whether any inspections are needed and if so whether it is GMP, GLP and/or GCP.

Where it is considered that one or more inspections are required make a cross-reference to the detail in sections on GMP, GLP, or GCP in the related Quality, Non Clinical, or Clinical reports.

The inspection request should be referenced in the relevant part of sections III and VI of this document.

**2.5. Type of application and other comments on the submitted dossier**

Indicate type of marketing authorisation application (reference to the legal basis of the application), for example:

- Article 8.3 of Directive 2001/83/EC, as amended – complete and independent application, (i.e. complete dossier with administrative, quality, non-clinical and clinical data)
- Article 10(4) of Directive 2001/83/EC, as amended – relating to applications for a biosimilar medicinal product
- Article 10a of Directive 2001/83/EC, as amended – relating to applications relying on well established medicinal use supported by bibliographic literature
- Article 10b of Directive 2001/83/EC, as amended – relating to applications new fixed combination products or Article 10c of Directive 2001/83/EC, as amended – relating to informed consent from a marketing
authorisation holder for an authorised medicinal product applications new fixed combination products

Indicate if acceptable justifications exist for waiving certain studies or replacing original studies by literature data. If certain studies are only available as publications it is important to clarify whether or not such studies are not of sufficient quality to allow an in depth assessment of crucial data.

Other potential types of legal basis coming from the Paediatric Regulation are Article 28 of Regulation (EC) No 1901/2006 or Article 30 of Regulation (EC) No 1901/2006.

Indicate if the applicant has requested accelerated assessment and the fulfilment of relevant criteria. See relevant CHMP guideline pursuant to article 14(9) of Regulation (EC) No 726/2004

Indicate if the applicant has requested a conditional marketing authorisation or an approval under exceptional circumstances (or if this is proposed by the Rapporteurs/CHMP). The assessment of the fulfilment of relevant criteria is an integrated part of this report (for further guidance, please see relevant EMEA/CHMP guidelines).

For Conditional approval, the rapporteur should assess the validity of the reason(s) put forward by the applicant according to the guideline for conditional Marketing Authorisation pursuant to Commission Regulation No 507/2006). In brief address the following: serious/life threatening disease; emergency threat; orphan product - positive R/B; medical need; does immediate availability outweighs the risks? For conditional approval the positive B/R is made pending results of further studies. Discuss those studies in terms of feasibility once the product is on the market.

For exceptional circumstances, the rapporteur should assess the validity of the reason(s) following those listed in Section 6 of Part II of the Annex to Commission Directive 2001/83/EC, as amended and the guideline for granting of a marketing authorisation under exceptional circumstances, pursuant to Article 14(8) of Regulation (EC) No 726/2004). In brief: address particularly the relevant indent (rarity, ethics or stage of scientific knowledge) and the type of specific obligations that may be necessary. For an approval under exceptional circumstances it is in principle not foreseen that the applicant can provide comprehensive data on efficacy and safety.

For similar biological medicinal products the relevant guidelines (EMEA/CHMP/437/04 Guideline on similar biological medicinal products, EMEA/CHMP/42832/2005 Guideline on similar biological medicinal products containing biotechnology derived medicinal products as active substances: non-clinical and clinical issues) and annexes and EMEA/CHMP/BWP/49348/05 Guideline on similar biological medicinal products containing Biotechnology-derived Proteins as Active Substance - Quality Issues have to be taken into consideration.
An extensive comparability exercise will be required to demonstrate that the similar biological and reference products already authorised in the community have similar profiles in terms of quality, safety and efficacy. Detailed information of the reference product (name) strength, pharmaceutical form, MAH, date of authorisation in EU and the detailed information (such as batch number and country of origin) of the batches used in the comparability exercise (quality, non-clinical and clinical): need to be provided in tabular format in the quality part of this report.

3. Scientific overview and discussion

GENERAL GUIDANCE

Although this report shall include the necessary details to understand what is in the file you are requested to focus on the salient findings from each part of the critical assessments on Q, NC, C, and Pharmacovigilance, with a discussion/interpretation of the results giving the grounds for the benefit-risk assessment and the CHMP recommendations and the questions posed to the applicant.

Tables and graphs to display results are encouraged.

The structure is in accordance with the LoQ AR, Day 150/180 AR and EPAR structure and shall thus be updated at the different stages of the CHMP review.

This is particularly important in view of the need for a CHMP AR at the time of a possible withdrawal.

If data from publications is used by the applicant or in the context of the assessment, a clear referencing should be included allowing for clear identification of the publications. Consider generation of a reference list if a substantial number of publications is used. If appropriate ensure clear expression of the view on the content of a publication (e.g. if used not only as data reference but in the context of a discussion).
3.1. Introduction

3.2. Quality aspects

3.2.1. Introduction

3.2.2. Active Substance

General Information

Manufacture, characterisation and process controls

Specification

Stability

Comparability exercise for Active Substance

3.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Manufacture of the product and process controls

Product specification

Stability of the product

Comparability exercise for Finished Medicinal Drug Product

Adventitious agents

GMO

3.2.4. Discussion on chemical, pharmaceutical and biological aspects

Since the preceding chapter is largely descriptive, a more focussed discussion is necessary here, in order to isolate important or interesting issues.

For each section, the consider addressing the following points:

1) Identify the most important findings and deficiencies described above (do not repeat results). Describe how results agree. 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 should be addressed
4) Highlight important issue that are expected for CHMP discussion
Otherwise for standard non-contentious products a standard wording may
be used as follows -
‘…Information on development, manufacture and control of the drug
substance and drug 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.’

3.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

3.3. Non clinical aspects

3.3.1. Pharmacology

3.3.2. Pharmacokinetics

3.3.3. Toxicology

3.3.4. Ecotoxicity/environmental risk assessment

3.3.5. Discussion on non-clinical aspects

The discussion is often the most important part of the assessment. In
terms of structure it should follow the presentation of the results
above.

Try to be as clear and concise as possible (often discussions are too
long and the true meaning of the data is not addressed).

For each section, the discussion should address the following points:

1) Identify the most important findings and deficiencies described above
(do not repeat results). Describe how results agree. 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 should be
addressed

4) Highlight important issue that are expected for CHMP discussion

For example, for each indent of the non-clinical part, consider
discussing the following:

- Are the data submitted in accordance with legal requirements,
available guidelines and scientific advice?
Discuss any justifications for waiving certain studies or replacing original studies by literature data.

- What major issues are raised (major objections and other important concerns)

- How are the issues expected to be resolved? For example, are further data or justifications required, is there a need for a Scientific Advisory Group or (related to the paediatric development) an Opinion from the PDCO?

- How are the findings (or lack of information) reflected in the SPC? Ensure correspondence with SPC (particularly 5.3 Preclinical safety data but also e.g., sections 4.3, contraindications, 4.5 Interactions, 4.6 Pregnancy and lactation, 5.1 Pharmacodynamic properties, sections 5.2 Pharmacokinetic properties, if relevant) and that all information in the SPC is explicitly assessed and supported by the scientific assessment.

- What key findings (or uncertainties) should be part of the benefit-risk assessment?

3.3.6. Conclusion on non-clinical aspects

A very brief summary of the conclusions drawn from the non-clinical documentation should be provided here.

The following “standard” wording could be considered: “Overall, the primary pharmacodynamic studies provided adequate evidence that .... The general pharmacology studies showed...... From the pharmacokinetic point of view, the ..... was the most relevant species for non-clinical efficacy and safety studies. Overall, the toxicology programme revealed.... This information has been included in the SPC.”

3.4. Clinical aspects

- Tabular overview of clinical studies

A tabular overview of all clinical studies submitted, including study number, design and, number and characteristics of patients in treatment arms (this table should be is in accordance with CTD table 2.7.3.1).

Consider also mentioning ongoing and planned studies for information if relevant for this indication.
3.4.1. Pharmacokinetics

3.4.2. Pharmacodynamics

3.4.3. Discussion on clinical pharmacology

Highlight the critical issues, which have been identified in the different sections of the report (absorption, distribution, elimination). Conclude on the quality of the pharmacokinetic documentation with special emphasis on identified deficiencies.

In addition, this section should contain assessment of how the pharmacokinetic information is reflected in the SPC and should especially reflect and substantiate statements made in relevant sections of the SPC. The assessor should discuss whether adequate information and/or precautions/restrictions have been included in the SPC in case of lack of information in certain groups of patients (renal/hepatic impairment, children, elderly etc.).

Highlight the critical issues that have been identified in the different sections of the report and conclude on the quality of the pharmacodynamic documentation with special emphasis on identified deficiencies.

Specific discussion points to be considered:

- **BE**: Discuss conclusions relating to bioequivalence or dosage adjustment in the SPC if necessary. - Lack of information in certain groups of patients (children, elderly women with childbearing potential etc.) should be mentioned to qualify statement made in section 4.4 of the SPC and it should be mentioned here and summarised in the overall conclusion if follow-up studies have been requested by the CHMP.

- **PK interaction studies**: Comments on interactions with other medicinal products, interaction with food (if not addressed under absorption or pharmacodynamic interaction above) and dynamic interactions should be provided if data are available. Separate clearly pharmacokinetic from pharmacodynamic interactions. Possible interactions with herbal remedies and the possible clinical implications.

- **Dose response studies**: Assess justification for surrogate endpoints and results outlining how these studies have contributed to confirmation of efficacy, e.g. acute diseases such as infectious diseases and pain may rely on fixed-dose studies in which case the points outlined under the next heading (“Main studies”) should be considered.

- Consider whether efficacy might be reduced in the older adult population due to PD changes.
3.4.4. Conclusions on clinical pharmacology

A very brief summary of the conclusions drawn from the clinical pharmacology documentation should be provided here.

3.4.5. Clinical efficacy

A table of the trials (number of studies and enrolled patients e.g. age gender and severity of disease etc) could be given here if not covered above. This table should be in accordance with CTD table 2.7.3.1 as appropriate.

Dose-response studies and main clinical studies

Summary of main efficacy results

A tabulated summary of the most relevant information to describe the efficacy data generated in the main trial(s) should be presented. This summary should be tailored to the data set which was used by the CHMP for its conclusion on efficacy. Therefore, it will be important to reflect the results from the analysis that was deemed most relevant (preferably (m)ITT and PP, but maybe also clinically defined sub-group [pre-specified or post-hoc], etc.). The pre-specified primary analysis should be presented in any case.

The following template table should be used to display the data for the specific studies. The level of detail should be adjusted to the data later needed for the discussion and conclusion on benefits, as well as the benefit-risk assessment. Treatment groups should be presented in separate cells, and so should be information on different analysis sets (e.g. ITT and PP). Reasons for drop-outs should be summarised.

Different main trials should be presented in separate tables. No additional text is foreseen in this section apart from these tables. A detailed description of these trials with for instance information on design and power calculation is presented in other sections. The safety data is subject to the section “Clinical safety”.

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>

<table>
<thead>
<tr>
<th>Study identifier</th>
<th>&lt;code&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>{as indicated on the study report}</td>
<td></td>
</tr>
</tbody>
</table>

Title: <title>
<table>
<thead>
<tr>
<th>Design</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>{describe key elements of the design (cross-over, parallel, factorial, dose-escalation, fixed-dose response) including randomization, blinding, allocation concealment, mono-/multi-centre, etc.}</td>
</tr>
<tr>
<td>Duration of main phase:</td>
<td>&lt;time&gt;</td>
</tr>
<tr>
<td>Duration of Run-in phase:</td>
<td>&lt;time&gt; &lt;not applicable&gt;</td>
</tr>
<tr>
<td>Duration of Extension phase:</td>
<td>&lt;time&gt; &lt;not applicable&gt;</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hypothesis</th>
<th>Overview and list of questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;Superiority&gt;</td>
<td>&lt;Equivalence&gt;</td>
</tr>
<tr>
<td>&lt;Non-inferiority&gt;</td>
<td>&lt;Exploratory: specify&gt;</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatments groups</th>
<th>Add as many rows as needed to describe the treatment groups</th>
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</thead>
<tbody>
<tr>
<td>&lt;group descriptor&gt;</td>
<td>&lt;treatment&gt;. &lt;duration&gt;, &lt;number randomized&gt;</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Endpoints and definitions</th>
<th>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</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;Co-Primary endpoint&gt;</td>
<td>&lt;label&gt;</td>
</tr>
<tr>
<td>&lt;Secondary other: specify&gt; endpoint</td>
<td>&lt;label&gt;</td>
</tr>
<tr>
<td>&lt;Secondary other: specify&gt; endpoint</td>
<td>&lt;label&gt;</td>
</tr>
</tbody>
</table>

| 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}

<table>
<thead>
<tr>
<th>Analysis description</th>
<th>Primary Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis population and time point description</td>
<td>Intent to treat</td>
</tr>
<tr>
<td>{consider adding a brief description of the definition of the population}</td>
<td>{as per above terminology}</td>
</tr>
<tr>
<td>Descriptive statistics and estimate variability</td>
<td>Treatment group</td>
</tr>
<tr>
<td>Number of subject</td>
<td>&lt;n&gt;</td>
</tr>
<tr>
<td>&lt;endpoint&gt; {label as above}</td>
<td>&lt;point estimate&gt;</td>
</tr>
<tr>
<td>{&lt;statistic&gt;} {e.g. mean, median, etc}</td>
<td></td>
</tr>
<tr>
<td>{&lt;variability statistic}&gt; {e.g. standard deviation, confidence interval, etc}</td>
<td></td>
</tr>
</tbody>
</table>
### Effect estimate per comparison

*{add as many rows as needed to describe the relevant statistical testing performed}*

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Comparison groups</th>
<th>Group descriptors</th>
<th>Test statistic</th>
<th>Point estimate</th>
<th>Variability statistic</th>
<th>Variability</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;Co&gt;-Primary endpoint</td>
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<tr>
<td>&lt;&lt;Co&gt;Primary &lt;&lt;Secondary&gt;&lt;Other: specify&gt; endpoint</td>
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<tr>
<td>&lt;&lt;Co&gt;Primary &lt;&lt;Secondary&gt;&lt;Other: specify&gt; endpoint</td>
<td></td>
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</tr>
</tbody>
</table>

### Notes

*{consider amongst others the following information: - reasons for drop-outs - critical findings with regard to the analysis}*

### Analysis description

*{repeat all the above sections for each analysis that is considered relevant}*

---

**Clinical studies in special populations**

In case of a specific clinical study in older people, the assessment should pay particular attention to the inclusion/exclusion criteria, as these could be defining an artificially healthy population. The table reporting older patient numbers is relevant for the majority of medicinal products. The Applicant should provide this table as part of the answers to the day 120 LoQ.
If the disease/condition is prevalent in older subjects, any specific PK studies and RCTs in older subjects should be presented or the absence of such studies should be acknowledged.

If PK in older people is likely to be altered, e.g. due to renal impairment, the need for dose adjustment should be discussed.

Statements made after consideration of these data should be meaningfully reflected in the product information.

**Analysis performed across trials (pooled analyses AND meta-analysis)**

**Supportive study(ies)**

3.4.6. Discussion on clinical efficacy

The discussion is often the most important part of the assessment report. In terms of structure it should in principle follow the flow of the presentation of results above.

Try to be as clear and concise as possible (often discussions are too long and verbose, and the true meaning of the data is not addressed).

For each section, the discussion should address the following points:

1) Identify the most important findings and deficiencies described above (do not repeat results). Describe how results agree. Summarise evidence for each conclusion.

2) Discuss if the data submitted fulfil the requirements (legal, guidelines, scientific advice)

3) Describe the major issues raised and to what extent they should be addressed

4) Highlight important issue that are expected for CHMP discussion

Both study design and results should be subject to the critical discussion. Be explicit about the view on key elements like choice of comparators, endpoints as well as shortcoming of the data. The following is a compilation of potential aspects to be addressed in such discussion.

**Design and conduct of clinical studies**

- Was the design of the studies adequate (randomised active and placebo controlled trials)? If not, what are the justifications and are they acceptable?

- Was the patient population adequately selected (reflection on inclusion/exclusion criteria)? Was there any age limit exclusion?

- Is the comparator considered appropriate? In case of an active comparator, discuss the relevance in view of the EU approved treatment options.
- Critical discussion of the appropriateness of the choice of endpoints as well as the duration of the study considering regulatory guidance/scientific advice. Validity of surrogate markers to replace hard endpoints? Acceptability of a composite endpoint and its domains?
- Adequacy of the methods, conduct, analysis and reporting of results from main studies, as appropriate. Discuss any particular issues raised regarding the study design.
- Is the design in accordance with legal requirements, available guidelines, scientific advice?
- What are the implications of any GCP inspection?

**Efficacy data and additional analyses**

- Magnitude and clinical relevance of the effect. Clinical relevance of the observed effect should be described since it may be particularly important for the benefit /risk assessment.
- What are the key findings (or uncertainties)? What key findings (or uncertainties) should be part of the benefit-risk assessment?
- Generalisability (external validity) of trial findings. Do the results support the claimed indication?
- Are any additional analyses required and what are the reasons for this request?
- If sub-group data is considered of particular relevance for the overall assessment of efficacy, this should be explained.
- What major issues were raised during the assessment (major objections and other important concerns)
- How are the issues expected to be resolved? For example, are further data or justifications required, is there a need for a Scientific Advisory Group or (related to paediatric data) an Opinion from the PDCO?
- Discuss any justifications for waiving certain studies or replacing original studies by literature data.
- Lack of information in certain groups of patients (children, elderly women with childbearing potential etc.) should be mentioned to qualify statement made in section 4.4 of the SPC and it should be mentioned here and summarised in the overall conclusion if follow-up studies have been requested by the CHMP.
- Which are specific considerations for the paediatric population?
- For similar biological medicinal products mention explicitly the comparative nature of the results obtained with the chosen reference medicinal product.
- How are the findings (or lack of information) reflected in the SPC? Ensure correspondence with SPC (particularly section 5.1) and that all information in the SPC is explicitly assessed and supported by the scientific assessment.
- Mention if there are any outstanding data, which remain as follow-up measures/SO and if this is reflected in the SPC.

3.4.7. Conclusions on clinical efficacy

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

3.4.8. Clinical safety

Patient exposure

Adverse events

Serious adverse events and deaths

Laboratory findings

Safety in special populations

This table is relevant for the majority of medicinal products: safety information should be reported specifically for the older population or its lack should be acknowledged.

When assessing data with regard to older adults, not only the number of included patients, but also the risk-benefit analysis should be considered, as specific potential risks should be taken into consideration (e.g. cognitive and cardio-vascular effects and influence on renal and hepatic function).

The risk-benefit assessment should take into account the epidemiology of the disease, the prevalence and severity of co-morbidities in older adults, available information on concurrent pharmacotherapy should be discussed, particularly when a potentiation of adverse effects could be expected in combination with concurrently administered drugs.

The knowledge of the safety profile of drugs of the same class should also be considered when defining the RMP, particularly when older patient numbers are low.
<table>
<thead>
<tr>
<th>MedDRA Terms</th>
<th>Age &lt;65 number (percentage)</th>
<th>Age 65-74 number (percentage)</th>
<th>Age 75-84 number (percentage)</th>
<th>Age 85+ number (percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total AEs</td>
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<td></td>
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<tr>
<td>Serious AEs – Total</td>
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<td></td>
<td></td>
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<tr>
<td>- Fatal</td>
<td></td>
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<tr>
<td>- Hospitalization/prolong existing hospitalization</td>
<td></td>
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<tr>
<td>- Life-threatening</td>
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<td></td>
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<td></td>
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<tr>
<td>- Disability/incapacity</td>
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<td></td>
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<tr>
<td>- Other (medically significant)</td>
<td></td>
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<td></td>
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<tr>
<td>AE leading to dropout</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Psychiatric disorders</td>
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<tr>
<td>Nervous system disorders</td>
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<tr>
<td>Accidents and injuries</td>
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<tr>
<td>Cardiac disorders</td>
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<tr>
<td>Vascular disorders</td>
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<tr>
<td>Cerebrovascular disorders</td>
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<tr>
<td>Infections and infestations</td>
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<tr>
<td>Anticholinergic syndrome</td>
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<tr>
<td>Quality of life decreased</td>
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<tr>
<td>Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures</td>
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<tr>
<td>&lt;other AE appearing more frequently in older patients&gt;</td>
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</tbody>
</table>

*The Applicant should provide this table as part of the answers to the day 120 LoQ. Statements made after consideration of these data should be meaningfully reflected in the product information.*
Immunological events

Safety related to drug-drug interactions and other interactions

Discontinuation due to AES

3.4.9. Discussion on clinical safety

The discussion is often the most important part of the assessment. In terms of structure it should follow the presentation of the results above.

Try to be as clear and concise as possible (often discussions are too long and verbose, and the true meaning of the data is not addressed).

For each section, the discussion should address the following points:

1) Identify the most import findings and deficiencies described above (do not repeat results). Describe how results agree. Summarise evidence for each conclusion.

2) State if the data submitted fulfil the requirements

3) Describe the major issues raised during the assessment (major objections and other important concerns) and to what extent they should be addressed.

4) Highlight important issue that are expected for CHMP discussion

5) Conclude and state what information should be reflected in the SPC and the opinion

6) What key findings (or uncertainties) should be part of the benefit-risk assessment?

Specific points for discussion

- Patient exposure: Discuss any limitations of the safety database in relation to the proposed target population.

- How are the findings (or lack of information) reflected in the SPC? Ensure correspondence with SPC (e.g., Sections 4.3, contraindications, 4.4 special warnings, 4.7 Effects on ability to drive and use machines 4.8 Undesirable effects, 4.9 Overdose, as appropriate) and that all information in the SPC is explicitly assessed and supported by the scientific assessment.

- Description of the safety profile of the medicinal product and degree of safety assessed

- Is the safety profile in accordance with that expected from non-clinical studies and known class effects?
Describe relevant safety aspects specific for the paediatric population by age group where appropriate. Link this closely to the recommendations in the SPC. Are there any specific (serious) ADRs and/or monitoring requirements?

- Sufficient long-term data? Mention if there are any outstanding data which remain as follow-up measures and if this is reflected in the SPC. Additional post-marketing studies/FUM?

- For similar biological medicinal products mention explicitly the comparative nature of the results obtained with the chosen reference medicinal product.

### 3.4.10. Conclusions on clinical safety

A brief statement about the conclusions that can be drawn from the clinical safety documentation should be provided here (e.g., most frequent adverse drug reactions and other significant safety issues).

### 3.4.11. Pharmacovigilance system

Elaborate as appropriate in concordance with points made in the critical assessment modules; an assessment of whether the system described appears to meet the needs for this particular product. Note whether the MAH has provided the requested proof that they have the services of a Qualified Person for pharmacovigilance and the necessary means to report adverse reactions.

Note that the future MAH must ensure that the system of pharmacovigilance is in place and functioning before the product is placed on the market and for as long as the marketed product remains in use.

Consider the following statements in the AR:

<The (Co)Rapporteur considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.>

If on the other hand there are outstanding items to be resolved in the pharmacovigilance system description and implemented before the medicinal product is put on the market, should be listed as questions in the LoQ at day 120 and/or ultimately as FUMs in the final Opinion/CHMP AR. If deficiencies have been identified with the description of the pharmacovigilance system or the availability of the QP and means to report adverse reactions, one of the following paragraphs should be stated depending upon the severity of the deficiencies.
<The (Co)Rapporteur considers that the Pharmacovigilance system as described by the applicant has the following deficiencies:<list the deficiencies>

<Provided that the deficiencies are rectified prior to the applicant placing the medicinal product on the market, the CHMP may consider that the Pharmacovigilance system will fulfil the requirements. The applicant must ensure that the system of pharmacovigilance is in place and functioning before the product is placed on the market>

3.4.12. Risk management plan

At Day 80 the CHMP rapporteur should have performed the first overall assessment of the application, together with identification of any major issues in the RMP. To assist the PRAC in the provision of their Advice it would be helpful for the CHMP rapporteurs to flag to the PRAC Rapporteur any particular issues and concerns that were identified during the assessment of the dossier that could impact the Risk Management Plan. This includes any particular nonclinical safety findings, gaps in the clinical pharmacology package, potential safety signals from the clinical trials, etc. At this stage it is particularly important that safety concerns are identified (important identified risks, important potential risks, important missing information). This is even more essential if these issues were not identified by the applicant in the dossier and are therefore unlikely to be reflected in the RMP.

The PRAC will provide the CHMP with its advice on the evaluation of the Risk Management Plan. This advice will in part be based on the assessments of the dossier by the (Co-)Rapporteur hence the Day 80 assessment reports will be an important source of information for the PRAC Rapporteur.

Once the PRAC Advice is received, this will be integrated into the draft D120 List of Questions for discussion by the CHMP. It is important to note that this PRAC Advice may also contain proposed questions on the Risk Management Plan to be added to the CHMP List of Questions. If the CHMP deviates from the PRAC advice then this will be discussed in the List of Questions (see guidance there).

**Issues and/or concerns for consideration by the PRAC Rapporteur when assessing the RMP:**

Provide issues and concerns that were identified during the overall assessment of the application and that should be considered in the assessment of the Risk Management Plan by the PRAC.

4. Orphan medicinal products

<According to the conclusion of the COMP (Opinion dated 00/00/00) the prevalence of the “condition” <state the condition> is <> per 10000 individuals in the EU>.
Indicate if, and when the product received Orphan Drug Designation related to the applied indication.

State the orphan indication and the prevalence of the condition (from COMP summary report).

Introduce the following statement as appropriate: <According to the conclusion of the COMP (Opinion dated 00/00/00) the prevalence of the “condition” <state the condition> is <> per 10000 individuals in the EU>.

For medicinal products similar to an orphan medicinal product; elaborations on similarity and on the data supporting clinical superiority to an already authorised orphan medicinal product in the same indication (refer to Commission Regulation (EC) No 847/2000. Article 3d: Definitions) are done in separate reports (Appendix).

Special consideration may have 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.

5. Benefit risk assessment

This section should be left blank.

This section is revised at each rapporteur or CHMP report (Day 120, Day 150 etc). The purpose is to provide an accurate snapshot of the key benefits and harms, of the strength of evidence and limitations of the data as they become evident, and about the benefit risk assessment in the light of the available evidence and therapeutic indication.

The benefit risk assessment represents the most crucial part of assessment report. In the earlier assessments, due to many unsettled issues it may difficult to fully appreciate the strength of evidence, so that the focus will be on the deficiencies and the resulting uncertainty. As the assessment matures, the key findings, strength of evidence and unresolved uncertainties will have been defined, and will be the basis for the conclusions on the benefit risk balance.

This section contains a mixture of factual key data and interpretation of the data trough value judgements.

Factual data and interpretation should be clearly separated. The factual presentation of key data is used as a basis before the benefit risk balance is made. The findings will have been described in much more detail in previous sections of the report. The summary should allow the reader to assess the key findings independently, i.e., in the absence of interpretation and value judgements. A clear distinction
between facts and interpretation is also a prerequisite to allow the reader to evaluate the intellectual processes and criteria that lead from the findings to the interpretation and conclusions on the benefit risk balance.

It is essential that this section is written as clearly as possible. Principles and relationships should be clearly stated. Statements and conclusions should be detailed and explicit. Conclusions should be justified in detail.

- Avoid repetition of what is stated elsewhere.
- Avoid that this section becomes the “summary of the summary”
- Focus on value judgements. Separate data from value judgment.

**Benefits**

This section should be left blank.

The purpose of the sections below (Beneficial effects, Uncertainty in the knowledge about the beneficial effects) is to mention the most important favourable effects of the product and the level of uncertainty about those effects.

Definition of a “favourable effect”: Any beneficial effect for the target population (often referred to as “benefit” or “clinical benefit”) that is associated with the product. These commonly include improvements in clinical efficacy but are not limited to efficacy (for example, a reduction in toxicity could also be a favourable effect). Do not repeat results extensively here, these are described in detail elsewhere. Just mention those key results and associated uncertainty.

**Beneficial effects**

In this section, describe the following:

- Shortly mention what are the beneficial effects that are of interest in this condition and for this type of agent. What are the important endpoints for measuring them?
- Conclude on what the data show in terms of such beneficial effects (point estimates, confidence intervals, etc.)
- Describe “overall” benefits and benefits in important subgroups (e.g. as defined by age, sex, ethnicity, organ function, disease severity, or genetic polymorphism).
- Consider also describing relative efficacy from pivotal studies, main benefits versus comparator, size of the effect and the statistical evidence. If no active- and placebo-controlled study submitted, is this justified?
- Highlight any specific aspects of formulation (composition or development) which impact the safe and effective use of the product.
• For medicinal products, which constitute a significant technical, scientific or therapeutic innovation (Article 3(2)b) describe the beneficial effect that are linked to this innovation (avoid any statements which could be used as promotional claims by the company).

• Highlight any specific aspects of formulation (composition or development) which impact the safe and effective use of the product.

• For medicinal products, which constitute a significant technical, scientific or therapeutic innovation (Article 3(2)b) describe the beneficial effect that are linked to this innovation (avoid any statements which could be used as promotional claims by the company).

**Uncertainty in the knowledge about the beneficial effects**

In this section, describe the following:

• Mention the main sources of uncertainty, e.g., variation, important sources of bias, methodological flaws or deficiencies (including GCP, compliance, etc.), unsettled issues.

• How do the supportive non-clinical and clinical data impact on the uncertainties? What are the assumptions and expectations (potential of the treatment)?

• Be explicit about the impact of any uncertainties in terms of, e.g., the plausible range of expected benefits given the uncertainties (not just confidence intervals).

• Mention if there are any sources of uncertainties with respect to (in-process) controls or stability, characterisation, manufacturing method, which could compromise batch to batch consistency and a constant efficacy profile (to be considered especially for negative opinions).

• For medicinal products, which constitute a significant technical innovation (Article 3(2)b) describe the uncertainties in knowledge of this innovation.

• Mention if there are any sources of uncertainties with respect to (in-process) controls or stability, characterisation, manufacturing method, which could compromise batch to batch consistency and a constant efficacy profile (to be considered especially for negative opinions).

• For medicinal products, which constitute a significant technical innovation (Article 3(2)b) describe the uncertainties in knowledge of this innovation.

**Risks**

This section should be left blank.
The purpose of the sections below (Unfavourable effects, Uncertainty in the knowledge about the unfavourable effects) is to mention the most important unfavourable effects of the product, both known and unknown, and the level of uncertainty about those effects. Do not repeat results extensively, these are described in detail elsewhere. Just mention the conclusions, i.e., which are the key unfavourable effects that have been observed or that are otherwise of concern even if (yet) unobserved.

Definition of “unfavourable effects”: Typically, this would include any detrimental effects (often referred to as “risks”, “harms”, “hazards” both known and unknown) that can be attributed to the product or that are otherwise of concern for their undesirable effect on patients’ health, public health; or the environment.

Unfavourable effects are not necessarily limited to safety endpoints. For example, unfavourable effects may also be loss of efficacy on some important efficacy endpoints or other undesirable effect.

**Unfavourable effects**

In this section, describe the conclusions on what are the important unfavourable effects based on the data submitted. Consider for example:

- **Important adverse drug reactions, their severity, duration and reversibility.**
- **Important pharmacokinetic and pharmacodynamic interactions**
- **Important unfavourable effects in terms of public health or the environment; potential for abuse and misuse.**
- **Consider also describing relative safety, compare the toxicity profile to standard of care, or drugs of the same pharmacological class**
- **Indicate if there is any quality specific aspect either in the active substance, in the finished product or related to a medical device which may lead to a safety concern (e.g. immunogenicity, ERA, etc...).**
- **Indicate if there is a risk to the environment especially for Genetically Modified Organism (GMOs).**
- **Indicate if there is any quality specific aspect either in the active substance, in the finished product or related to a medical device which may lead to a safety concern (e.g. immunogenicity, ERA, etc...).**
- **Indicate if there is a risk to the environment especially for Genetically Modified Organism (GMOs).**
**Uncertainty in the knowledge about the unfavourable effects**

In this section, describe the following:

- Limitations of the data set, e.g., due to sample size, study design, duration of follow-up, and implications of such limitations with respect to predicting the safety of the product.
- Important quality issues, non-clinical safety findings and their impact on the safety. How do these data impact on the uncertainties?
- Be explicit about the impact of any uncertainties, lack of safety data, and unknowns on the description of the safety profile.
- For medicinal products, which constitute a significant technical innovation (Article 3(2)b) describe the uncertainties in knowledge about the unfavourable effect.
- For medicinal products, which constitute a significant technical innovation (Article 3(2)b) describe the uncertainties in knowledge about the unfavourable effect.

**Effects Table**

**Table X.** Effects Table for [insert product name and indication] (data cut-off: ...).

<table>
<thead>
<tr>
<th>Effect</th>
<th>Short Description</th>
<th>Unit</th>
<th>Treatment</th>
<th>Control</th>
<th>Uncertainties/Strength of evidence</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favourable Effects</td>
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<td>Unfavourable Effects</td>
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</table>

**Abbreviations:**

**Notes:**

*General guidance for constructing an effects table (ET)*

- The purpose of the effects table is to improve consistency, transparency, and communication of the benefit-risk assessment by summarising the key benefits and risks together with their...
uncertainties. Its role is to separate the main study results, as described in the benefit-risk section of the assessment reports, from the assessment of the overall benefit-risk balance to facilitate the discussion. This is achieved by providing a compact and consistent display of the key effects including all uncertainties and limitations that may affect their clinical interpretation, without any statements regarding their relative importance. It should be emphasised that the ET should not replace the inclusion of quantitative data in the benefit-risk section of the assessment reports.

- The ET should be used for initial applications of new active substances (excluding generics and biosimilars) and for important extension of indication applications.

- Initially, the ET should appear only in the Rapporteur’s Day 80 report. Subsequently, it should be merged at Day 120 List of Questions and kept updated throughout the assessment until the CHMP Day 210 report. Eventually, it should be included in the EPAR. If there are changes to a claimed indication during the assessment, the ET should reflect such changes. The final ET should reflect the final indication and mention only the data and uncertainties relevant to the approved target population.

**Table format**

- The ET provides a tabular representation of the main outcomes that drive the benefit-risk discussion with all the important favourable and unfavourable effects on the rows and the clinical effect size estimates together with a description of the associated uncertainties on the columns. In particular, the following columns are included in an ET (see the table below for a template):

  - **Effect column**: Provides an acronym or very short identifier of the effect (e.g. RR for response rate).
  
  - **Description column**: Provides a very short description of how the effect was measured. If needed, further description is included in the footnotes (e.g. by a reference to the literature).
  
  - **Unit column**: Displays the unit of measurement for each effect (e.g., mmHg, months, %).
  
  - **Treatment group columns**: Summarize the key effects of the index drug driving the benefit-risk discussion. (A) separate column(s) is (are) included for each relevant control group for which sufficient clinical data are available (e.g., placebo, different dosages of the new substance, active controls). If needed, reference(s) to the specific studies describing the effect can be included in the footnotes.
• **Uncertainties column:** Briefly describes the strength of evidence and any major uncertainty or limitation for each effect.

• **References column (optional):** For effects where particularly complex issues have arisen, this column provides a reference to the relevant part of the text, e.g., number major objection or other concern, risk-minimisation measure, SmPC section.

**Effects**

• As the ET serves to complement the narrative in the benefit-risk balance section of the assessment report, it should contain the key favourable and unfavourable effects that are mentioned in this part of the assessment report, including the uncertainties.

• An important aspect to consider when deciding which of the available study outcomes to include in the ET is the need to be complete without being overly precise. In practice, this can often be achieved by including the primary efficacy endpoints and additionally those secondary endpoints that are considered to be of most clinical relevance (i.e., the key secondary endpoints). In terms of safety, this would often include the most important side effects. Should there be large quantitative differences between a primary or key secondary endpoint and a clinically less relevant secondary endpoint, then these discrepancies can briefly be mentioned in the uncertainties column of the ET.

**Effect size estimates**

• The ET should provide as much as possible integrated (“pooled”) data rather than being a detailed repetition of the results from individual studies. The focus should be on the main studies that drive the evidence of the benefit-risk discussion. If needed, reference(s) to the specific studies describing the effects can be included in the footnotes (see also example below). Where possible, the degree of statistical uncertainty should be quantified by providing standard errors or confidence intervals. If relevant, indirect comparisons should also be included (e.g., results from single arm trials compared to historical data).

• Information from multiple studies should be displayed as effect estimate ranges (e.g., the mean change from baseline from three clinical trials that is 1.1, 1.3 and 1.4, can be represented as a range from 1.1 to 1.4), unless it is possible to provide some aggregated statistic (e.g., pooled data). In some situations with multiple studies, information from the most important study is sufficient and supportive studies may be briefly described under “Strength of evidence” (see Uncertainties column, below).

• Sometimes, the dossier includes multiple pivotal studies conducted in different patient populations or with different treatment regimens or combinations, each requiring individual benefit-risk
assessments. In such situations, it may be necessary to provide separate effect size estimates for each of these populations, especially for those effects that differ significantly across these populations. The rationale for displaying these data separately is that the benefit-risk assessment can vary among the different populations. For example, such differences could ultimately result in a restriction of the indication should a positive MA recommendation be provided. It can also translate into different indications. When both benefits and risks need to be assessed separately for each indication, then separate tables can be considered.

Uncertainties column

- The purpose of the uncertainties column is to provide a brief mentioning of important strengths or weaknesses of the data. For surrogate endpoints, this column can also be used to express how these data should be interpreted clinically by describing the potential/expectations of the treatment in terms of relevant clinical outcomes. Also, if the interpretation of the data indicates an overestimation or underestimation of an effect, a short explanation can be provided and, if possible, a corrected estimate or range of values. Finally, the reasoning may be explained where it is not possible to interpret the estimates for a key effect in the light of all the evidence and uncertainties.

- For instance, direct evidence, rigorous methodology, consistent results, precise and unbiased estimates, or very low p-values could be emphasized to reflect strong evidence. Weak evidence could be described in terms of serious limitations of the study, indirect evidence, inconsistent results, imprecise methods, important likely biases, etc. Only main weaknesses and strengths should be highlighted. More extensive explanation should be provided in the body of the text, in particular the result sections on uncertainties of benefits and risks preceding the ET.

ET Example

- An example of ET is provided below based on a selection of the favourable and unfavourable effects presented in the narrative of the benefit-risk section of the EPAR EMEA/H/C/002445 published on 28 November 2012.

**Table 1. Hypothetical ET for lixisenatide for treatment of adults with type 2 diabetes mellitus to achieve glycaemic control in patients not adequately controlled on oral antidiabetics (data cut-off ....).**

<table>
<thead>
<tr>
<th>Effect</th>
<th>Description</th>
<th>U</th>
<th>LIX</th>
<th>PBO</th>
<th>EXE</th>
<th>Uncertainties/ Strength of evidence</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Favourable Effects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c</td>
<td>Mean change in HbA1c from baseline</td>
<td>%</td>
<td>-0.79 (1)</td>
<td>-0.19 (1)</td>
<td>-0.83 (2)</td>
<td>-0.39 (2)</td>
<td>The effect of lixisenatide was more pronounced in Asian patients compared to Caucasian patients. The lower effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(-0.95,-0.63)</td>
<td>(-0.43,0.05)</td>
<td>(-0.83)</td>
<td>(-0.39)</td>
<td></td>
</tr>
</tbody>
</table>
### Effect Description | U | LIX | PBO | EXE | Uncertainties/Strength of evidence | Refs.
--- | --- | --- | --- | --- | --- | ---
Effect | | | | | in Caucasians is partly explained by a large placebo effect especially in some geographical regions. | (3)
Body weight | Mean change in body weight from baseline kg | -0.79 | -0.51, -0.28 | -0.75 | -0.75 | -0.75 | -0.75 | in Caucasians is partly explained by a large placebo effect especially in some geographical regions. | (3)
Unfavourable Effects
Nausea | Incidence of nausea % | 26.9 | 7.3 | 2.7 | Approximately 70-80% of the patients experiencing nausea or vomiting completed the treatment. | (5)
Vomiting | Incidence of vomiting % | 11.4 | 2.7 | 5.3 | 1.9 | 0.4 | <0.1 | (5)
Diarrhoea | Incidence of diarrhoea % | 11.1 | 8.0 | 7.9 | 4.8 | 1.6 | 1.6 | Hypoglycaemia is mainly seen when lixisenatide treatment is combined with sulfonylurea. | (5)
Hypo-glycaemia | Incidence of hypo-glycaemia % | 1.7 | 7.0 | 2.5 | 7.9 | 15.2 | 15.2 | Hypoglycaemia is mainly seen when lixisenatide treatment is combined with sulfonylurea. | (5)
ISRs | Incidence of ISRs % | 5.3 | 1.9 | 0.4 | <0.1 | (5)
Allergic reactions | Incidence of allergic reactions % | 0.4 | <0.1 | (5)
Palpitations | Incidence of palpitations % | 1.5 | 0.7 | (5)
Tachycardia | Incidence of tachycardia % | 0.7 | <0.1 | (5)

Abbreviations: U: unit; LIX: lixisenatide; PBO: placebo; EXE: exenatide; kg: kilograms; ISRs: injection site reactions; Hypo: hypoglycaemia; #: number of cases.

Notes: (1) EFC6018; (2) Pooled data from the two placebo-controlled add-on studies with metformin (EFC6014 and EFC10743); (3) Data from the exenatide-controlled add-on study with metformin (EFC6019); (4) Data from the placebo-controlled add-on study with sulfonylurea (EFC6015); (5) Pooled data from all phase 2/3 controlled studies.

**Balance**

This section should be left blank.

The purpose of the sections below (Importance of favourable and unfavourable effects, Benefit-risk balance) is to describe if the favourable effects, with their uncertainties, outweigh the unfavourable effects, with their uncertainties. In extreme cases (very obvious excess of favourable effects or vice-versa and low uncertainty about the effects), this section can be relatively short. In less extreme cases, particularly when many favourable and unfavourable effects accompanied by their uncertainties need to be balanced simultaneously, more detail is needed in order to make the logic of decision-making as explicit as possible.
**Importance of favourable and unfavourable effects**

In this section, describe the importance of the effects (a qualitative description of how much you value the effects, express “value judgements”, “clinical relevance”) and compare the favourable effects among each other. Identify those favourable effects that are most important.

“Importance” should generally be described in qualitative terms. How does the observed effect compare to the minimum effect that is worthwhile detecting for a certain patient outcome, in a disease-specific context? For example, “Generally, given the poor prognosis in terms of survival in the context of this advanced cancer setting, an improvement in median overall survival in the order of 2-3 months is considered of clinical relevance. The 6 month difference in median overall survival observed was considered to be very important from a clinical point of view.” Importance may also be expressed in terms of how the product addresses an unmet medical need, need for active treatments (for example, “although a number of agents have shown activity in terms of response rate, this is the first product to show an improvement in overall survival”) or role in therapy (for example, “a treatment that improves overall survival may be very valuable for patients that are in good condition and can tolerate more aggressive treatment”).

Similarly, compare unfavourable effects among each other and identify those that are most important.

**Benefit-risk balance**

In this section describe the following:

- Compare all the important favourable effects against all the important unfavourable effects.

- Explain how the combined favourable effects are judged to exceed (or to fail to exceed) the combined unfavourable effects. What would be the minimum favourable effects needed to balance against the important unfavourable effects? How does this compare to the results observed?

**Discussion on the benefit-risk assessment**

In this section, describe the following:

- Describe how the balance of favourable and unfavourable effects changes depending on the uncertainties. For example, a high uncertainty in terms of important favourable effects may generally reduce their value. In terms of unfavourable effects, however, a high uncertainty about the safety will generally increase concerns about certain safety aspects.
• If the information is available, describe how the value judgements could change depending on the perspectives of different stakeholders (physicians, patients, etc.).

• Is the benefit-risk balance expected to be the same over the time of treatment?

• Discuss different expert views if available

• Discuss the need for restrictions to product availability or usage, or any other conditions or measures aiming to improve the benefit-risk balance

• Discuss the need for further studies

• Conclude on the overall “benefit-risk balance” for the whole indication, and for different subgroups of the indication if necessary

• If the benefit-risk balance is considered positive only for a restricted indication compared to the one applied for, discuss the reasoning for this restriction.

• Discuss regulatory options for approval (standard marketing authorisation, conditional marketing authorisation, authorisation under exceptional circumstances). If needed, elaborate on the detailed reasons (scope, requirements) for conditional approval or an approval under exceptional circumstance

5.1. Conclusions

The overall B/R of <name of product> <is> <positive> provided <general statement on conditions>; is <negative>.

The overall B/R of <name of product> <is> <positive> provided <general statement on conditions>; is <negative>.

6. List of questions as proposed by <Co->Rapporteur

Definitions of questions:

“Major objections”, preclude a recommendation for marketing authorisation. In principle, one major objection may entail more than one question and the use of bullet points or subheadings is encouraged. It is vital that the structure and content of a major objection are clear and understandable to the reader. Detailed comments may be necessary along with a reference to guidance documents.
Ideally, the objection should include a clarification as to what kind of response/action is expected from the applicant.

“Other concerns”, may affect the proposed conditions for marketing authorisation and product information. For example, if there are no data in renally impaired patients, new data may resolve this question whereas lack of such data may lead to amendments in the SPC/follow-up measures. Other concerns should be resolved before approval; failure to do so may render the application un-approvable.

Try to limit the other concerns to what is needed to know.

(Make cross-references from the actual question to what is stated in the scientific discussion)

All issues identified should be asked to the company in order to resolve them before the opinion. No Post-Approval Commitments should be proposed at this phase of the assessment.

6.1. Quality aspects

Major objections

Drug substance

In addition, mention if there are additional major objections on the drug substance concerning the confidential / closed part of an EDMF. These will be detailed in an annex to the main Quality Report.

Drug product

Other concerns

Drug substance

In addition, mention if there are additional concerns on the drug substance concerning the confidential / closed part of an EDMF. These will be detailed in an annex to the main Quality Report.
Drug product

6.2. Non clinical aspects

Major objections

Pharmacology

Pharmacokinetics

Toxicology

Other concerns

Pharmacology

Pharmacokinetics

Toxicology
6.3. **Clinical aspects**

**Major objections**

**Pharmacokinetics**

**Pharmacodynamics**

**Efficacy**

**Safety**

**Pharmacovigilance system**

**Risk management plan**

**Other concerns**

**Pharmacokinetics**

**Pharmacodynamics**

**Efficacy**

**Safety**

**Pharmacovigilance system**

**Risk management plan**

6.4. **New active substance**

7. **Recommended conditions for marketing authorisation and product information**

_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 (SPC, PL, labelling)”. The results of the user consultation or the justification for not having them should however be addressed._

7.1. **Conditions for the marketing authorisation**

_For example legal status, conditional marketing authorisation, exceptional circumstances/specific obligations and other follow-up measures. Details of the risk management plan._
7.2. **Summary of product characteristics (SmPC)**

If specific comments are warranted, these should be incorporated in the complete version of the original SPC highlighting the proposed changes. Any comments should be put in a boxed area within the text.

7.3. **Labelling**

If specific comments are warranted, these should be incorporated in the complete version of the original labelling highlighting the proposed changes. Any comments should be put in a boxed area within the text.

7.4. **Package leaflet (PL)**

*User consultation*
8. QRD guidance and 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

- "Operational procedure on Handling of "Consultation with target patient groups” on Package Leaflets (PL) for Centrally Authorised Products for Human Use

- "Consultation with Target Patient Groups-meeting the requirements of Article 59(3) without the need for a full test—Recommendations for Bridging"

- "Position paper on user testing of package leaflets"
**Product information**

<table>
<thead>
<tr>
<th>Name of the medicinal product:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Name and address of the applicant:</td>
<td></td>
</tr>
<tr>
<td>Name of company which has performed the user testing:</td>
<td></td>
</tr>
<tr>
<td>Type of Marketing Authorisation Application:</td>
<td></td>
</tr>
<tr>
<td>Active substance:</td>
<td></td>
</tr>
<tr>
<td>Pharmaco-therapeutic group (ATC Code):</td>
<td></td>
</tr>
<tr>
<td>Therapeutic indication(s):</td>
<td></td>
</tr>
<tr>
<td>Orphan designation</td>
<td>□ yes □ no</td>
</tr>
</tbody>
</table>

---

**Rapporteur/CoRapporteur**

- Full user testing report provided □ yes □ no
- Focus test report provided □ yes □ no
- Bridging form provided\(^1\) □ yes □ no

\[^1\] QRD form for submission and assessment of user testing bridging proposals [EMA/355722/2014]

[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 form\(^1\) has been provided, please perform the assessment in the bridging form and state the overall conclusion/recommendations below:

  ________________________________________________________________
  ________________________________________________________________
  ________________________________________________________________
  ________________________________________________________________

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

- 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]

______________________________________________________________________________
______________________________________________________________________________
______________________________________________________________________________
______________________________________________________________________________
______________________________________________________________________________

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 make 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

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 document on the content of the <Co-> Rapporteur day 80 critical assessment report
Overview and list of questions
EMA/90842/2015
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 □ yes □ no
  (e.g. 16 out of 20 participants)
  □ 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 document on the content of the <Co-> Rapporteur day 80 critical assessment report Overview and list of questions EMA/90842/2015
Guidance regarding Conclusions

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?
9. Appendices

9.1. Day 80 AR on similarity dated <   >
9.2. Day 80 AR on clinical superiority <   >
9.3. Day 80 AR in response to a claim <for 1 year of data exclusivity for the specific new indication in accordance with Article <10(5)> <74(a)> of Directive 2001/83/EC, as amended
9.4. **QRD guidance and checklist for the review of user testing results**