[insert only for CHMP/CAT adopted doc & add EMA header and footer]
Amsterdam, <insert full date>
<insert Doc. Ref.>
<Committee for Medicinal Products for Human Use (CHMP)>< Committee for Advanced Therapies Medicinal Products (CAT)>

<Co>Rapporteur day<60*><80> critical assessment report

Overview and list of questions

Or<DRAFT> <CHMP><CAT> day <90*><120> list of questions

**in case of accelerated assessment*

<Invented name>

<Active Substance>

Procedure No. EMEA/H/C/<XXX> For EU-M4all, procedure number is EMEA/H/W/xx

Applicant: <xxx>

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

<CHMP><CAT> Rapporteur:	
<CHMP><CAT> Co-rapporteur:	
<CHMP coordinator(s)> *to be included only for CAT procedures*	
PRAC Rapporteur:	
EMA PL:	
Start of the procedure:	
Date of this report:	
Deadline for comments:	

Note to the (Co)Rapporteurs: Assessment reports and comments should be circulated VIA EUDRALINK. Product Shared Mailbox: product.name-xxxx@ema.europa.eu and product initial MAA dedicated mailbox:

MAAxxxx@ema.europa.eu (xxxx refers to the product number EMA/H/C/xxxx) should always be copied.

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

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

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

Suggested font: Verdana 9.

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

Table of Contents

Administrative information

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

Only in case of accelerated assessment: **<In accordance with Article 6(3) of Regulation (RC) No 726/2004, I the (Co) Rapporteur hereby declare that I have completed my assessment report in less than 80 days>.**	**Date** **Signature**

Declarations

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

☐ Yes

☐ No

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

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

Whenever the above box is un-ticked please indicate section and page where confidential information is located (including the Product Information document) here:

List of abbreviations

1. <Co><Rapporteur><CHMP> <CAT> Recommendations

Based on the review of the data on quality, safety, efficacy, the application for <product name> <an orphan medicinal product> in the treatment of <claimed indication>

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

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

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

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

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

<Deficiencies arising from concerns over the confidential (ASM - Active Substance Manufacturer restricted) part of the DMF are mentioned in the appendix (this appendix is not supplied to the MAA). These concerns will be conveyed in confidence to the holder of the DMF.>

Indicate how this recommendation is made with regard to the Conditional Approval/ Exceptional circumstances opinion, as appropriate and in line with the discussion on comprehensiveness of clinical data submitted in the marketing authorisation application, as per guidance in section 5.7.3, and the discussion on the elements of comprehensive data that are not available in the submitted dossier.

1.1. 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).

1.2. Inspection issues

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

1.2.1. GMP inspection(s)

[For pre-approval inspections to verify GMP compliance]

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

And/or

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

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

1.2.2. GCP inspection(s)

[For routine GGP inspections]

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

And/or

[For triggered GCP inspections]

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

1.3. <New active substance status>

[Not applicable for biosimilars and EU-M4all]

Based on the review of the data, it is considered that the active substance <active substance> contained in the medicinal product <product name> <is> <could be> <is not> qualified as a new active substance <provided that satisfactory responses are given to the concerns as detailed in the List of Questions>.

1.4. <Additional data exclusivity /Marketing protection >

[Not applicable for EU-M4all]

For applications including a new indication, for which the applicant claimed an additional year of marketing protection in accordance with Art 14(11) of Regulation (EC) No 726/2004 – new indication submitted within the 8 first years of a MA or one year of data exclusivity in accordance with Art 10(5) of Directive 2001/83/EC - new indication for a well established substance <Taking into account the provisions of <Article 14(11) of Regulation (EC) No 726/2004> <Article 10(5) of Directive 2001/83/EC>, it <is considered> <could be considered> <is not considered> that *[For Art 14(11)]*<the new therapeutic indication brings significant clinical benefit in comparison with existing therapies> *OR [For Art 10(5)]* that <the <pre-clinical tests> <and> <clinical studies> carried out in relation to the new indication were significant> <provided that satisfactory responses are given

to the concerns as detailed in the List of Questions>.<The major objections identified, which preclude the recommendation are detailed in the List of Questions.>

[For applications including a legal status switch, for which the applicant claimed an additional year of data exclusivity:]

Taking into account the provisions of Article 74(a) of Directive 2001/83/EC, it is considered> <could be considered> <is not considered> that the <pre-clinical tests> <and> <clinical trials> submitted in support of the classification of {specify medicinal product name} as 'medicinal product not subject to medical prescription' are significant <provided that satisfactory responses are given to the concerns as detailed in the List of Questions>. <The major objections identified, which preclude the recommendation are detailed in the List of Questions.>

1.5. <Similarity with authorised orphan medicinal products>

[Not applicable for EU-M4all]

It is considered that <name of product> <is> <could be> <is not> similar to <name of authorised orphan medicinal products> within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000 <provided that satisfactory responses are given to the concerns as detailed in the List of Questions>.

1.6. <Derogation(s) from market exclusivity>

[Not applicable for EU-M4all]

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

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

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

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

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:

Justification	**Assessment**
Specific derogations foreseen in the legislation, with particular reference to Annex I of Directive 2001/83/EC, as amended	Mention specific derogations and confirm the reasons why the application fulfils the conditions for applying them.
Specific derogations foreseen in guidelines, with particular reference to ICH/CHMP or EC guidelines	Mention guidelines and specific derogations, and give reasons why the application fulfils the conditions for applying them.
Due to the extent of scientific knowledge the conduct of certain clinical trials is considered unethical[1-2], 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)	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 biosimilarity assessment (in case of biosimilars) or benefit/risk assessment and provision of adequate information to patients and prescribers

[1] Requirements of GCP principles of Directive 2001/20/EC, Directive 2005/28/EC and Directive 2001/83/EC as amended by Directive 2003/63/EC

[2] Requirements of GCP principles of Directive 2001/20/EC, Directive 2005/28/EC and Directive 2001/83/EC as amended by Directive 2003/63/EC (Declaration of Helsinki provides a useful reference also)

[3] Council Directive on Animal Welfare 86/609/EEC and Council Decision on the European Convention of the Protection of Vertebrae Animals.

Note: For generic and hybrid applications (chemicals) a special template for the Day 80 AR has been developed.

This template is applicable for line extensions and fixed dose combinations

In the case of a Biosimilar development, the development strategy chosen by the company should be described, justified and assessed in view of the relevant guidelines. Guidance specific to biosimilars (limited to the scope of authorisation for the reference product) is included in this template. The guidance in this template is given for biosimilar applications relying on indications of the reference product (not introducing a new indication). This text should be read in conjunction with the general guidance.

2.1. Problem statement

For biosimilars: Section 2.1 and subsections 2.1.1 to 2.1.5 are not applicable.

2.1.1. Disease or condition

[not applicable for biosimilars]

- *State the claimed therapeutic indication.*

The purpose of this section is to be clear about the therapeutic indication(s) that are being claimed and assessed. It may be useful to explain any technical terms or definitions in the wording of the indication that are not standardized. For example if the indication is "treatment of advanced colorectal cancer" it may be useful to explain that this means locally advanced (T4) or metastatic (M1) colorectal cancer as defined in the AJCC/UICC TNM Classifications System, 7th edition (2009).

2.1.2. Epidemiology <and risk factors, screening tools/prevention>

[not applicable for biosimilars]

- *Shortly describe the epidemiology of the disease (e.g., incidence, mortality).*

The purpose of this section is to describe the disease burden, which is related to the unmet medical need.

Include statistics (e.g., incidence, mortality) in the EU or outside EU if relevant (e.g., EU-M4all applications for products that are intended exclusively for markets outside of the European Union). Simply referring to worldwide statistics or statistics in other regions may not be informative.

The description should be as specific as possible to the therapeutic indication described above. High-level textbook introductions to a particular therapeutic area should be avoided. For instance, if the therapeutic indication is for the treatment of adult patients with

relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, there is no need to describe the epidemiology of multiple myeloma in general in great in detail, just focus on the specific clinical situation.

Societal or public health implications of the condition (e.g., impact of poor control and prevention of an infectious disease) should also be addressed if relevant.

2.1.3. <Biologic features><Aetiology and pathogenesis>

[not applicable for biosimilars]

- *Focus on what is relevant for the scientific assessment (e.g., pathophysiology relevant for mechanism of action).*

Describe briefly only if relevant for the therapeutic indication, e.g., certain mutations targeted by available treatments or mutations conferring resistance or heterogeneity of subpopulations. There is no need to describe in detail all the new insights into the molecular pathology and genomics of the condition unless this is strictly relevant for the scientific assessment.

Describe significant limitations or uncertainties in the understanding of the condition or therapy.

2.1.4. Clinical presentation, diagnosis <and stage/prognosis>

[not applicable for biosimilars]

- *Be as specific as possible to the claimed therapeutic indication (avoid high-level textbook introduction to a particular disease).*

The purpose of this section is to describe the natural history of the disease, particularly in terms of symptoms and prognosis.

Describe briefly and only as relevant for the therapeutic indication.

2.1.5. Management

[not applicable for biosimilars]

- *Describe aims and main methods of treatment, incl. surgery, medical therapy, etc. Refer to clinical guidelines and other published references.*
- *Describe the unmet medical need.*

Focus on the benefits and risks of the main treatments that are relevant for the evaluation of the application in the relevant indication. The purpose is to describe the unmet medical need for the relevant indication. If the claimed therapeutic indication is substantially changed during the evaluation, e.g., restriction of indication, this section may need editing.

Describe aims and main methods of treatment, incl. approved drugs in the EU and elsewhere. There is no need to extensively describe all the available literature; a few references to main publications or clinical guidelines are generally sufficient. Beware of vague statements and opinions about the available treatment options (unless these can be adequately supported by facts and adequately referenced), as the assessment reports formally reflect the Rapporteurs' or CHMP the scientific assessment. For instance, avoid stating that "products have been approved for treatment of the condition but the benefits are modest", unless the benefits of these products have been specifically assessed or described by others as such, and reference can be made, e.g., to an EPAR or a publication. Often a factual description based on clinical guidelines and other published references is sufficient.

This section should not include information on the benefits and risks of the applicant's medicinal product.

Hypothetical example of section 2.1. Problem statement

Note, this extensive example is for illustration purposes only. In many situations, particularly in case of well-known conditions, this section can be relatively short, focussing on the unmet medical need.

2.1.1 Disease or condition

Treatment of relapsed/refractory multiple myeloma. Patients with relapsed/refractory disease are defined as patients with relapsed, "primary refractory" or "relapsed-and-refractory" disease according to the International Myeloma Working Group (IMWG) classification:

- Relapsed Disease: Previously treated myeloma patients who, after a period of being off-therapy, require salvage therapy but do not meet criteria for "primary refractory" or "relapsed-and-refractory" categories, as outlined below.
- Refractory Disease: MM that is non-responsive while on therapy or progresses within 60 days of last therapy. Relapsed-and-refractory myeloma is defined as relapse of disease in patients who achieve minor response (MR) or better, and then either become non-responsive while on salvage therapy, or progress within 60 days of last therapy. Primary refractory myeloma refers to patients who have never achieved an MR with any therapy.

2.1.2 Epidemiology and risk factors, screening tools/prevention

Multiple myeloma (MM) is a rare and incurable disease that accounts for 10% of all haematological malignancies. In Europe, there are approximately 27,800 new cases each year. The median age of patients at diagnosis is 65 years and the disease has a typical course characterised by a chronic phase lasting several years, and an aggressive terminal phase. The prevalence was estimated to be approximately 1.3 people in 10,000. (Globocan, 2008) This is equivalent to a total of around 66,000 people in the EU. Almost all patients with multiple myeloma (MM) who survive initial treatment will eventually relapse and require further therapy.

2.1.3 Biologic features

Hypothetical example of section 2.1. Problem statement

Note, this extensive example is for illustration purposes only. In many situations, particularly in case of well-known conditions, this section can be relatively short, focussing on the unmet medical need.

Multiple myeloma is characterized by marrow plasmacytomas (plasma cell tumours) and overproduction of monoclonal immunoglobulins (IgG, IgA, IgD or IgE) or Bence-Jones protein (monoclonal K or h light chains), while the production of normal immunoglobulin is impaired. (Beers, 1999)

The cause of a myeloma cell's failure to differentiate is unknown. However, translocations between chromosome 14q32 and its neighbours (involving the immunoglobulin heavy chain region) and deregulation of the c-myc oncogene appear to play a role in the initial stages of the disease; additionally, mutations in N-ras and K-ras are seen in up to 15% of patients at the time of diagnosis. Conversely, mutations in p53 are rarely seen at diagnosis but instead are noted in extramedullary relapses, along with phenotypic and cytological changes. With the exception of chromosome 13q deletions, which are consistently associated with a poor prognosis, the role of other changes in the pathogenesis and severity of the disease have yet to be defined.

2.1.4 Clinical presentation, diagnosis and stage/prognosis

The clinical features of MM are varied and can arise from the effects of the tumour itself, or the toxicity of the tumour products, or the host's own response.

The most common symptoms include persistent unexplained skeletal pain (especially pain in the back or thorax), recurrent or persistent bacterial infection, anaemia, renal impairment, fractures and vertebral collapse, hypercalcaemia and, in some patients, hyperviscosity syndromes, neurological disease and clotting abnormalities (Beers, 1999; Smith, 2005). Approximately 20% of patients are symptom free and are diagnosed by chance (Desikan, 2000).

The most common criteria used in diagnosis of symptomatic MM are the presence of neoplastic plasma cells comprising greater than 10% of BM cells or presence of a plasmacytoma; paraprotein (M protein) in the serum and/or urine; and evidence of related organ or tissue impairment due to plasma cell disorder.

A clinical staging system, developed by Durie and Salmon (Durie, 1975), is useful for predicting survival of multiple myeloma patients and is used for prognosis (Harousseau, 2008). Combining a number of biological parameters of prognostic importance with serum albumin has led to a new International Staging System (ISS) (Greipp, 2005).

The prognosis depends on a variety of factors including age and stage of MM at time of diagnosis. Due to the availability of new agents in recent years including thalidomide, bortezomib and lenalidomide, and autologous stem cell transplant (ASCT), the 5-year survival rate has improved to 40% - 50%.

Despite progress in its current treatment and management, MM remains incurable. Although ASCT has extended survival in newly diagnosed MM, practically all patients eventually relapse.

Hypothetical example of section 2.1. Problem statement

Note, this extensive example is for illustration purposes only. In many situations, particularly in case of well-known conditions, this section can be relatively short, focussing on the unmet medical need.

(Harousseau, 2006), (Attal, 2003) In addition, approximately two thirds of newly diagnosed patients aged > 65 years are ineligible for this treatment (Palumbo, 2006). The treatment option for the majority of the MM population, i.e., the more fragile and elderly patients, is associated with low response rate and short survival. (Smith, 2005), (Smith, 2001), (Myeloma Trialists' Collaborative Group, 1998), (Palumbo, 2006)

In relapsed/refractory MM, despite salvage therapy, median overall survival (OS) remains poor (in the range of 30 months). Although patients with relapsed disease can achieve responses to subsequent anti-myeloma regimens, the duration of response typically decreases with successive relapses until resistant disease develops.

2.1.5 Management

The management of patients with relapsed/refractory disease represents a clinical challenge, as these patients suffer from continuing symptoms, complications of the disease (including renal failure, blood cytopenia or recurrent infections) and decreased quality of life. These patients typically receive salvage therapy until the next relapse or progression of disease or the development of intolerable toxicity and then go onto the next salvage option.

For the treatment of relapsed/refractory MM, conventional-dose chemotherapy and high-dose chemotherapy with stem cell support remain the current standard of care, along with supportive care including bisphosphonates (Palumbo, 2008b).

Treatment options are limited to three classes of agents (chemotherapy, IMiDs, and proteasome inhibitors) used in various combinations and schedules. Depth and duration of response are shorter than for newly-diagnosed patients and decrease with each line of therapy as drug resistance develops (NCCN 2014):

- Vincristine, doxorubicin and dexamethasone (VAD) or a related infusional regimen such as vincristine, adriamycin, methotrexate and prednisone (VAMP) or VAMP + cyclophosphamide (C-VAMP) have been most widely used. These regimens are associated with a high response rate and a CR rate of 10–25% (based on negative routine electrophoresis) (Smith, 2005).
- Pegylated doxorubicin (Caelyx) is approved in combination with bortezomib for the treatment of progressive multiple myeloma in patients who have received at least one prior therapy and who have already undergone or are unsuitable for bone marrow transplant.
- Bortezomib (Velcade) is indicated as monotherapy for the treatment of progressive multiple myeloma in patients who have received at least 1 prior therapy and who have already undergone or are unsuitable for bone marrow transplantation. It is used either alone or in combination with dexamethasone or chemotherapy (Harrousseau, 2008), although these combinations are not approved. In a trial where bortezomib was compared to dexamethasone, combined complete and partial response rates of 38%, and CR rates of 6% were reported with median times to progression (TTP) of 6 months for bortezomib

Hypothetical example of section 2.1. Problem statement

Note, this extensive example is for illustration purposes only. In many situations, particularly in case of well-known conditions, this section can be relatively short, focussing on the unmet medical need.

(Richardson, 2005).

- Lenalidomide (Revlimid) in combination with dexamethasone is indicated for the treatment of multiple myeloma patients who have received at least one prior therapy. Median TTP was for lenalidomide plus dexamethasone versus treatment of dexamethasone (11 months versus 5 months) (Dimopopoulos, 2007), (Weber, 2007).

Notes

The checklist above (for example *"☐ Describe the unmet medical need."*) is provided for guidance during drafting of the report - please delete the checklist from the final report.

In some situations and therapeutic areas, deviation from the recommended content and structure is necessary (e.g., vaccines, radio-pharmaceutical precursors, analogues, bio-similar medicinal products).

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.

For biosimilars: State in this section that [X] has been developed as a biosimilar to the reference product [Y], the claimed therapeutic indication(s) and if the applicant is claiming all or only part of the approved indications of the reference product.

2.3. The development programme/compliance with 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 recommendation and 7. of this document.

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

2.5.1. Legal basis

The legal basis for this application refers to:

For all submissions: Choose one among the following options:

<Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.>

<Article 10(a) of Directive 2001/83/EC, as amended – relating to applications relying on well established medicinal use supported by bibliographic literature.>

<Article 10(b) of Directive 2001/83/EC, as amended – relating to applications for new fixed combination products.>

<Article 10(4) of Directive 2001/83/EC, as amended – relating to applications for biosimilar medicinal products.>

<Article 58 of Regulation (EC) No 726/2004, - complete and independent application, by analogy to Article 8(3) of Directive 2001/83/EC.>

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

For extension(s) of marketing authorisation without grouping:

Indent(1) refers to Changes to the active substance(s), not defined as new active substance:

Indent (2) refers to Changes to strength, pharmaceutical form and route of administration as follows:

(a) change of bioavailability;

(b) change of pharmacokinetics e.g. change in rate of release;

(c) change or addition of a new strength/potency;

(d) change or addition of a new pharmaceutical form;

(e) change or addition of a new route of administration

For a grouping of extension of MA and variations:

<Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations>

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/are not of sufficient quality to allow an in depth assessment of crucial data.

2.5.2. <PRIME>

Indicate if PRIME eligibility was granted – information can be found in the list of PRIME products on EMA website:

«prodname» was granted eligibility to PRIME on <date> in the following indication: ***<insert the indication for which PRIME was granted***.

2.5.3. <Accelerated assessment>

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.

<The CHMP <and CAT> <agreed> <did not agree> to the applicant's request for an accelerated assessment as the product was <not> considered to be of major public health interest. This was based on *{include summary of reasons for accepting or rejecting accelerated assessment}*.>

If the accelerated assessment is no longer appropriate the (Co)Rapporteur/CHMP/CAT should propose to revert to standard timetable:
<However, it is no longer appropriate to pursue accelerated assessment, as *{include summary of reasons for reverting to standard timetable}*.>

2.5.4. <Conditional marketing authorisation>

[not applicable for biosimilars]

Indicate if the applicant has requested a conditional marketing authorisation (or if this is proposed by the Rapporteurs/CHMP/CAT). The assessment of the fulfilment of relevant criteria is an integrated part of this report (for further guidance, please see relevant EMA/CHMP guidelines). This section should document the applicant claims whilst the Rapporteur considerations on the acceptability of a CMA should be documented in Section 5.7.3.

<The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of the above mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive.
- It is likely that the applicant will be able to provide comprehensive data. *{Summarise in general terms the applicant's claim that they provide comprehensive data}*
- Unmet medical needs will be addressed, as *{include the applicant's claim on why the product will provide major therapeutic advantage over the authorised methods. When assessment of major therapeutic advantage over existing methods is needed, avoid the expression 'significant benefit', in particular for orphan medicines as it has a distinct regulatory meaning in the context of the parallel COMP assessment of maintenance of the orphan drug designation.}*.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. *{Summarise the applicant's claims}*>

2.5.5. <Marketing authorisation under exceptional circumstances>

[not applicable for biosimilars]

For exceptional circumstances, the (Co)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. This section should document the applicant claims whilst the Rapporteur considerations on the acceptability of a MA under exceptional circumstances should be documented in Section 5.7.3.

<The applicant requested consideration of its application for a Marketing Authorisation under exceptional circumstances in accordance with Article 14(8) of the above mentioned Regulation based on *{summarise the applicant's claims}.*>

2.5.6. <Biosimilarity>

For biosimilars the relevant guidelines should be considered (EMEA/CHMP/437/04 Rev. 1 Guideline on similar biological medicinal products, EMEA/CHMP/42832/2005 Rev. 1 Guideline on similar biological medicinal products containing biotechnology derived medicinal products as active substances: non-clinical and clinical issues, EMEA/CHMP/BWP/247713/2012 Guideline on similar biological medicinal products containing Biotechnology-derived Proteins as Active Substance: quality issues). Relevant Product class specific guidelines are also available on the EMA website.

Detailed information of the reference product (name) strength, pharmaceutical form, MAH, date of authorisation in EU has to be provided. Highlight any differences in strength, pharmaceutical form, or formulation of the intended biosimilar relative to the reference product.

<The chosen reference product is:

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

- Product name, strength, pharmaceutical form:
- Marketing authorisation holder:
- Date of authorisation: (dd-mm-yyyy)
- Marketing authorisation granted by:

□ <Union>

- <Member State (EEA): *{identify Member State}*
  - National procedure
  - MRP/DCP>
- Marketing authorisation number:

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

- Product name, strength, pharmaceutical form:
- Marketing authorisation holder:
- Date of authorisation: (dd-mm-yyyy)
- Marketing authorisation granted by:

□ <Union>

- <Member State (EEA): *{identify Member State}*
  - National procedure
  - MRP/DCP>
- Marketing authorisation number:

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which comparability tests and studies have been conducted:

- Product name, strength, pharmaceutical form:
- Marketing authorisation holder:
- Date of authorisation: (dd-mm-yyyy)
- Marketing authorisation granted by:

□ <Union>

- Member State (EEA): {identify Member State}
  - National procedure
  - MRP/DCP>

- Marketing authorisation number(s):
- Bioavailability study number(s):

2.5.7. <Additional data exclusivity/ marketing protection>

[not applicable for biosimilars and EU-M4all]

This refers to requests for an additional year of marketing protection for "new indication submitted within the 8 first years of a MA" (article 14(11) of Regulation (EC) No 726/2004), as well as one year data exclusivity for "a new indication for a well-established substance" (article 10(5) of Directive 2001/83/EC) and "change of classification of a medicinal product" (article 74a of Directive 2001/83/EC). Separate reports are also requested here (to be included as Appendix).

<The applicant requested consideration of one year <data exclusivity> <marketing protection> in regards of its application for a <new indication> <for a change in the legal status classification> in accordance with <Article 10(5) of Directive 2001/83/EC> <Article 74a of Directive 2001/83/EC><Article 14(11) of Regulation (EC) 726/2004>. <Assessment of this claim is appended.>

2.5.8. <New active substance status>

[Not applicable for biosimilars and EU-M4all]

[This section has to be filled out in case the applicant has claimed that the compound is a new active substance, either 'in itself' or in comparison to a substance previously authorised as a medicinal product in the European Union.]

<The applicant requested the active substance {*active substance*} contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.>

[or]

<The applicant requested the active substance {active substance} contained in the above medicinal product to be considered as a new active substance in comparison to {active substance} previously authorised in the European Union as {*name of the medicinal product authorised*}, as the applicant

claimed that {*active substance*} differs significantly in properties with regard to safety and/or efficacy from the already authorised active substance.>

[or]

<The applicant requested the radiopharmaceutical substance <*active substance* > to be considered as a new active substance as <it is a constituent not previously authorised in a medicinal product in the European Union> <the coupling mechanism to link <*active substance*> and <the radionuclide> <the ligand> has not been authorised previously in the European Union>.>

<Assessment of this claim is appended.>

2.5.9. Orphan designation

[For biosimilars and EU-M4all: section not applicable.]

<Not Applicable.>

or

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

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

2.5.10. Similarity with orphan medicinal products

[Not applicable for EU-M4all]

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

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

2.5.11. <Derogation(s) from orphan market exclusivity>

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

<The application contained a claim addressing the following derogation laid down in Article 8(3) of the Regulation (EC) No. 141/2000; <the holder of the marketing authorisation for the original orphan medicinal product has given his consent to the applicant> or < the holder of the marketing

authorisation for the original orphan medicinal product is unable to supply sufficient quantities of the medicinal product> or <the applicant can establish in the application that the medicinal product, although similar to the orphan medicinal product already authorised, is safer, more effective or otherwise clinically superior.> Assessment of these claims is appended.>

2.5.12. <Information on paediatric requirements>

1) Paediatric requirements apply – Note: the Decision number below has a format P/X/XX. Do not mention the date.

<Pursuant to Article <7> <8><30> of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) *[insert decision number(s)]* on <the agreement of a paediatric investigation plan (PIP)> *OR* <the granting of a (product-specific) waiver> <and> <on the granting of a class waiver>.

Only if a PIP included, i.e. not if there is a waiver:

<At the time of submission of the application, the PIP *[insert decision number for the PIP eligible to the reward]* was <completed> <not yet completed as some measures were deferred>.>

[Note: the following sentence to be included only in case of the PIP eligible to the reward (please check the PIP reference with the paediatric coordinator) being fully completed and a PDCO Opinion on compliance is available; compliance with a PIP not fully completed (i.e. in which case the PDCO only issues a letter and compliance report) should not be indicated here:]

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

2) Paediatric requirements do not apply (eg. Biosimilars and EU-M4all): If paediatric requirements do no apply at all to the concerned application, select the statement hereafter:

<Not applicable>

3. Scientific overview and discussion

The content of this section will be updated at the different stages of the CHMP/CAT review (Day 80/150/180/CHMP/CAT AR/EPAR) so as to constitute a self-standing document. It should therefore be sufficiently detailed to eventually be used for the CHMP/CAT (Withdrawal) AR and (W)EPAR and give sufficient justifications for the LoQ/LoOI as appropriate.

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 or biosimilarity assessment for biosimilars and the CHMP recommendations and the questions posed to the applicant.

Tables and graphs to display results are encouraged.

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. Quality aspects

The purpose of the Overview Quality AR is to support the scientific opinion and recommendation issued by the CHMP. In order to achieve that it should present in a brief, summarised way those details necessary to understand what is in the application for the MAA and sufficiently address the conclusions of the evaluation. The focus should be on the significant and noteworthy findings and aspects from the critical assessments on Quality as detailed and captured in the Quality AR.

A self-standing and focused elaboration is expected in order to allow the reader comprehensive understanding of the relevant findings affecting the benefit-risk assessment. The Overview should be a brief summary of the quality AR and should focus on the main conclusions and discussion/interpretation of the results giving the grounds for the benefit-risk assessment, the CHMP recommendations and/or the questions, especially the Major Objections (MO),raised to the applicant should be included in a concise and succinct manner. The level of detail would depend on the complexity of the product and the quality of the dossier.

For each section, consider addressing the following points:

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

2) State if the data submitted fulfil the requirements.

3) Describe the major issues raised and to what extent they have been/should be addressed.

4) Highlight important issues that need to be/have been discussed during CHMP (or BWP/QWP) meetings.

The structure of the document is in accordance with the LoQ AR, Day 150/180 AR and EPAR structure and should thus be updated at the different stages of the CHMP review. The Overview is not intended as a history of the assessment and instead it should rather reflect the status at each milestone of the evaluation procedure. Nevertheless in this context it may be useful and indeed more meaningful to reflect how the most controversial points of each application have been addressed and resolved, for example resolution of MOs, or how the AS

/FP specification or the control strategy has evolved/changed during the evaluation.

This is particularly important in view of the need for a CHMP AR at the time of a possible withdrawal and access to document requests.

Please note that for simplicity, not all CTD headings are reproduced in the report structure that follows, only the 'main' headings. Assessors may add more, or less, depending upon the complexity of the product; please also refer to the CTD guidance text for the applicant. In addition, note also that the CTD terms 'Drug Substance' and 'Drug Product' are synonymous with the EU legislative terms 'Active Substance' and 'Finished Product' respectively.

There should be a link between the recommendations (REC) for future development (CHMP AR 2.2.6) and the scientific discussion. Wherever such a REC is proposed, details can be given in 3.1.4. Discussion and conclusions section.

In case quality issues have been identified for inclusion in Annex II as conditions, they need to be well motivated in the CHMP AR, and should be explained in the context of a positive benefit-risk balance.

Refer to this link http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000037.jsp for more information regarding Annex II conditions and recommendations.

The aim of this guidance document is to cover chemical products and biological products (e.g. recombinant proteins). It is not expected to fully cover ATMPs but can still be used as a guide. It is also not intended to be used as a checklist but rather as assistance to the assessor to critically distil the quality AR into a succinct and comprehensive summary.

KEY:

AS: active substance

FP: finished product

Unboxed Text: *applicable to all products.*

Text in boxes: *specific to chemical or biological products as indicated.*

3.1.1. Introduction

The following text may be used:

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

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

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

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

3.1.2. Active Substance

3.1.2.1. General Information

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

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

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

Mention whether a CEP or ASMF procedure or full information in the dossier of the AS in the dossier is used.

Bio:
Consider to include key structure components such as number of amino acids and molecular size, glycosylation/post-translational modifications, "artificial" modifications (amino-acid substitutions, pegylation). Highlight and discuss elements of structure important for mechanism of action.

3.1.2.2. Manufacture, process controls and characterisation

Description of manufacturing process and process controls

Chem:

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

Very brief description of synthesis (one paragraph); if more than one source, discuss the differences in the synthetic routes and how these potentially may affect or not the product. Comment on alternate processes if proposed.

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

Briefly reflect the discussion regarding the definition of the starting materials (SMs) and if the arguments are acceptable. If MO were raised discuss if these have been resolved and how (e.g. by redefinition or by justification). Specify the critical steps and, if applicable, discuss the acceptability of specifications for intermediates.

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

Bio:

Mention the manufacturers of the active substance. Include a summary (one paragraph) of the main manufacturing process steps (e.g. fermentation (fed-batch or continuous), purification (e.g. chromatography steps), virus removal/inactivation (e.g. SD treatment (reagents/incubation time & temperature); nanofiltration (filter name/pore size)). The acceptability of process parameter ranges and IPC´s are discussed in connection to the overall control strategy below in this section.

When relevant, comment on local adaptations of the process if proposed to be run at different sites and how it has been shown that the different sites deliver material of the same quality.

Describe the generation of the cell banks and comment on whether they have been appropriately tested according to relevant guidelines.

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

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

Bio:

Process validation:

Include a short description of the process validation/ verification studies as applicable and discuss if they are adequate e.g. type of studies, scale, models used and cover the proposed commercial process. Describe any proposals for continuous process verification or concurrent validation if applicable.

Manufacturing process development

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

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

If Design Space (DS) is claimed, clearly state if it is acceptable, describe which process steps it covers, at which scale the DS was

developed and explain whether verification of the DS is needed at commercial scale.

Chem:

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

Bio:
Present an outline of the comparability exercise for the active substance (i.e. changes in the manufacturing process throughout development, site transfers etc.). Highlight any issues with the way the comparability exercise was designed and conducted taking into account in particular differences between pivotal clinical batches and what is intended for commercial production.

Discuss briefly the results and any uncertainties and provide a clear conclusion.

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

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

Characterisation

Briefly describe the characterisation studies of the Active Substance structure and potential impurities.

Chem:

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

3.1.2.3. Specification, analytical procedures, reference standards, batch analysis, and container closure

Specifications

Discuss whether the proposed AS specifications limits, tests and methods are acceptable. A table of the current specifications should be included.

Discuss the acceptability of the proposed acceptance criteria, mention briefly how they have been established/ justified and if this is in accordance with ICH Q6A and Q6B as appropriate. Discuss if the acceptance criteria of stated impurities have been justified based on general ICH thresholds where applicable or qualified in non-clinical and clinical studies or clinically justified by other means as appropriate.

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

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

Chem:

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

Summarise changes introduced during the evaluation (e.g. tightening of specifications) and state if further data are required leading to any recommendations (REC) to amend specifications when further batches will have been produced e.g., review of specifications.

Chem:

Discussion regarding specific impurities or other materials (catalysts, residual solvents etc.) should be included if specific issues need to be reflected.

Bio:
if testing for certain impurities (e.g. DNA, Protein A etc.) has been omitted from the specifications, briefly discuss the data provided to support this.

Analytical procedures and reference standards

Discuss whether the proposed procedures have been satisfactorily validated and if they are adequate to control the AS on a routine basis, i.e. as a release test. Consider elaborating on specialised / pivotal methods e.g. potency assays. Comment on the adequacy of information regarding the reference standards or materials.

In case of analytical method flexibility, mention the method for which it is requested and if it is acceptable.

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

Batch analysis

Include a comment on the adequacy of batch analysis results, the batch size of the tested batches and batch-to-batch consistency.

Container closure

Describe the container closure system for the active substance and its compliance with relevant requirements.

3.1.2.4. Stability

Chem:
clearly state the re-test period and storage conditions.

Bio:

clearly state the maximum storage period and storage conditions.

Discuss whether stability studies / conditions were according to ICH guidelines and, if not, if they are acceptable.

Comment on the scale of batches and their representativeness of the commercial product.

Discuss the stability results and if they showed any significant changes or trends. Discuss if the observed physical and chemical changes are likely to have a significant effect on efficacy and safety of the product when stored for the proposed shelf life under recommended conditions.

If any out of specification results were observed, mention the conclusions in this respect.

Discuss if photostability study complies with ICH Q1B and mention the conclusions.

Mention the outcome of forced degradation/stress studies and discuss if analytical methods are stability indicating and if they are the same or different as those used for routine analysis; if different comment if the methods were sufficiently validated.

State if further stability data are required leading to a REC.

3.1.3. Finished Medicinal Product

3.1.3.1. Description of the product and Pharmaceutical Development

Description of the product

Describe the finished product (pharmaceutical form, strengths and differentiation thereof, physical appearance, devices) and solvent (if included in the product package). A table detailing the qualitative and quantitative composition of the finished product should be included. The function of each ingredient should be indicated.

Indicate any overage or overfill.

Pharmaceutical development

Briefly describe the rationale behind formulation development and highlight if there are special features (e.g. whether QbD elements have been used). Discuss whether the choice of pharmaceutical form/strength adequately addresses the clinical needs (i.e. QTPP; bioavailability, patient's compliance, ease of administration, dosing regimen, target population (e.g. paediatrics) etc.).

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

Discuss whether the chosen formulation adequately accommodates the active substance's physicochemical properties (stability, incompatibilities, solubility, route of administration etc.). Discuss the differences (if any) and their relevance between the intended commercial formulation and those used during clinical studies.

Especially discuss any key characteristics of excipients, novel excipients (if present), adjuvants, excipients of biological origin etc.

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

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

Highlight the main aspects of manufacturing process development and summarise relevant studies (e.g. how critical process parameters have been identified). Mention if QbD elements have been used in the pharmaceutical development/ manufacturing development / process design (risk assessment, prior knowledge, DoE to support Design Space, etc.); provide a short summary of those and confirm if the approach is acceptable.

If QbD, consider including the most appropriate statement:

"The applicant has applied QbD principles in the development of the finished product and their manufacturing process.

a) However, no design spaces were claimed for the manufacturing process of the finished product.

or

b) Design spaces have been proposed for several steps in the manufacture of the finished product. The design spaces have been adequately verified."

Discuss any site transfers during pharmaceutical development.

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

Bio:
Studies aimed at demonstrating comparability between the commercial manufacturing process and earlier versions of the manufacturing process, between different manufacturing sites, or between different formulations (e.g. lyophilised versus liquid) should be summarised.

If the medicinal product includes components which are classified as medical devices (e.g. needles, catheters, etc.), discuss whether they comply with the relevant medical devices legislation. In accordance

with Article 117 of the Medical Device Regulation (EU) 2017/745, where a medicinal product is used in combination with a single-use integral medical device, applicants should provide the relevant documentation from a Notified Body (Opinion or EU certificate) confirming compliance of the device with the relevant General Safety and Performance Requirements in Annex I.

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

3.1.3.2. Manufacture of the product and process controls

Manufacture

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

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

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

Process controls

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

Discuss the adequacy of the overall control strategy, including whether process parameters and in-process controls are adequately set to control the process leading to consistent quality.

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

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

Process validation / verification

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

3.1.3.3. Product specification, analytical procedures, batch analysis

Specifications

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

Discuss the acceptability of the proposed acceptance criteria, mention briefly how they have been established and comment on whether these are sufficiently justified. Indicate if the identified impurities and other relevant quality attributes have been studied in non-clinical and clinical studies and if the related acceptance criteria are qualified as appropriate. Discussion on specific impurities or other attributes may be included if any issues need to be reflected.

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

Analytical procedures and reference standards

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

Discuss whether the proposed procedures have been satisfactorily validated and if they are adequate to control the finished product on a routine basis, i.e. as a release test.
Comment on the adequacy of information regarding the reference standards or materials.
In case a QbD approach is followed in support of analytical method flexibility, mention the method for which it is requested and if it is acceptable.

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

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

Batch analysis

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

Container closure

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

3.1.3.4. Stability of the product

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

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

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

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

Chem:
Mention stability studies outside the primary container, only if such data/information has been submitted (should not be requested otherwise) (relevant e.g. for tablets).

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

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

Discuss results from in-use stability studies if relevant.

Discuss results from photostability and stress studies.

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

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

Bio:

3.1.3.5. <Biosimilarity>

Present an outline of the comparability exercise performed at the quality level.

Detailed information (such as batch number and country of origin) of the batches used in the comparability exercise (quality, non-clinical and clinical) should be provided in tabular format if possible.

Highlight any issues with the design of the comparability exercise (e.g number of batches, scale, choice of reference, parameters compared, methods used, QTPP etc).Discuss how the reference ranges were established (number of batches, statistical tools etc.). Discuss if batches used in the biosimilarity exercise are representative of the commercial process.

If a global development approach has been followed confirm whether acceptable bridging between non-EU comparator and EU reference medicinal product has been presented.

Present the results of the comparability exercise in a tabular format, including quality attributes compared, analytical method used and key findings (see example below).

<Insert/Delete the table as appropriate>

Molecular parameter	Attribute	Methods for control and characterization	Key findings
Primary structure	Amino acid sequence	Reducing peptide mapping (MS)	Identical primary sequence
Higher order structure	Secondary and tertiary structure	CD spectroscopy	Comparable higher order structure
…			

Discuss the results of the comparability exercise and any uncertainties, how they are linked with S/E aspects and provide a clear conclusion on whether comparability at the Quality level has been sufficiently demonstrated.

3.1.3.6. Post approval change management protocol(s)

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

3.1.3.7. Adventitious agents

Provide details and conclusions from the presented information on viral safety in relation to starting materials, adequacy of virus removal steps and virus validation studies.

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

3.1.3.8. GMO

Provide the conclusions on environmental risk assessment relating to GMO products.

3.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

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

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

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

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

- Is there sufficient stability data to ensure safe use?

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

Indicate if a paediatric formulation has been developed or is to be developed. Indicate in which paediatric age groups the formulation would be used. Indicate if there is a need to request an Opinion from the PDCO.

Bio:

For biosimilars, conclude if the available quality data support biosimilarity versus the EU reference medicinal product. In addition, if applicable, conclude if any non-EU comparator used in pivotal clinical trials is representative of the EU reference medicinal product.

At the time of a positive Opinion:

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

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

product should have a satisfactory and uniform performance in the clinic."

- In case quality issues have been identified for inclusion in Annex II as conditions, use the following statement. Any measure identified as a condition needs to be well motivated in the CHMP AR, notably the need for a condition should be explained in the context of a positive benefit-risk balance:

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

Plus, if relevant:

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

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

3.2. Non-clinical aspects

3.2.1. Introduction

3.2.2. Pharmacology

3.2.2.1. Primary pharmacodynamic studies

3.2.2.2. Secondary pharmacodynamic studies

3.2.2.3. Safety pharmacology programme

3.2.2.4. Pharmacodynamic drug interactions

3.2.3. Pharmacokinetics

3.2.4. Toxicology

3.2.4.1. Single dose toxicity

3.2.4.2. Repeat dose toxicity

3.2.4.3. Genotoxicity

3.2.4.4. Carcinogenicity

3.2.4.5. Reproductive and developmental toxicity

3.2.4.6. Toxicokinetic data

3.2.4.7. Tolerance

3.2.4.8. Other toxicity studies

3.2.5. Ecotoxicity/environmental risk assessment

Only the reliable/accepted results should be included in the table.

Where data are not provided, not accepted nor required, the corresponding row should be deleted.

Summary of main study results

Substance (INN/Invented Name):			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 or …		Potential PBT (Y/N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}		B/not B
	BCF		B/not B
Persistence	DT50 or ready biodegradability		P/not P
Toxicity	NOEC or CMR		T/not T
PBT-statement:	The compound is not considered as PBT nor vPvB		

	The compound is considered as vPvB The compound is considered as PBT				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)		µg/L			> 0.01 threshold (Y/N)
Other concerns (e.g. chemical class)					(Y/N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106 or …	K_{oc} =			List all values
Ready Biodegradability Test	OECD 301				
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = $DT_{50, sediment}$ = $DT_{50, whole\ system}$ = % shifting to sediment =			Not required if readily biodegradable
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC		µg/L	species
Daphnia sp. Reproduction Test	OECD 211	NOEC		µg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC		µg/L	species
Activated Sludge, Respiration Inhibition Test	OECD 209	EC		µg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF		L/kg	%lipids:
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$			for all 4 soils
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect		mg/ kg	
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC		mg/ kg	
Earthworm, Acute Toxicity Tests	OECD 207	NOEC		mg/ kg	
Collembola, Reproduction Test	ISO 11267	NOEC		mg/ kg	
Sediment dwelling organism		NOEC		mg/ kg	species

3.2.6. 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.

For biosimilars, introduce the comparability strategy of the applicant and the comparability in vitro and in vivo performed.

Discuss the results of the comparability exercise conducted against the chosen reference medicinal product in light of available scientific guidelines on biosimilars. Non-clinical data should also be correlated to data provided in the quality section, where relevant (for example, afucosylation levels of Fc glycans).

Discuss the quality of the tests performed, their validation, the number of representative batches used and discuss if all the modes of actions have been compared to support all the (claimed) indications. Discuss the results and if there are differences in the functionality, if those differences are susceptible to be significant or not.

Discuss non-clinical bridging data if applicable. If a global development approach has been followed confirm whether acceptable bridging between non-EU comparator and EU reference medicinal product has been presented.

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 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, comment if the non-clinical study program was build up by the risk-based approach i.e. with possible omission of in vivo studies.*
3. *Describe the major issues raised and to what extent they should be addressed*
4. *Highlight important issue that are expected for CHMP discussion*
5. *Highlight the key findings pointing towards a demonstration of similarity, together with the drawbacks noted during the evaluation. Discuss if the issues spotted are considered relevant in the biosimilarity exercise or if they can be considered as acceptable and provide some rationale to support your opinion.*

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. [not applicable for biosimilars]

- *What key findings (or uncertainties) should be part of the benefit-risk assessment, or biosimilarity assessment for biosimilars?*

Conclusions on ERA:

Choice of minimal standard sentences:

For active substances that are exempted from assessment according to the guideline (vitamins, electrolytes etc.):

<The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, {*active substance*} is not expected to pose a risk to the environment.

For substances considered to be potential PBT (persistent, bioaccumulative and toxic) and/or vPvB (very persistent, very bioaccumulative) or with specific concern (e.g. endocrine disruptors), outcome of the specific assessment is added to the standard conclusion on a case-by-case basis.

For active substances that remain in Phase I:

{*Active substance*} PEC surfacewater value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5.

or for substances already on the market:

{*active substance*} is already used in existing marketed products and no significant increase in environmental exposure is anticipated *[based on justification]*.

Therefore {*active substance*} is not expected to pose a risk to the environment.

For active substances that reach Phase II (see table):

{*Active substance*} is not a PBT substance or if PBT add a specific conclusion according to the PBT assessment.

- Considering the above data, {*active substance*} is not expected to pose a risk to the environment.

- Considering the above data, {*active substance*} should be used according to the precautions stated in the SPC in order to minimize any potential risks to the environment.

For dossiers requiring additional ERA data:

As a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of {*active substance*} to the environment.

<Assessment of paediatric data on non-clinical aspects>

3.2.7. 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."

For biosimilars, conclude if the available non-clinical data support biosimilarity versus the EU reference product. In addition, if applicable, conclude if any non-EU comparator is representative of the EU reference medicinal product.

3.3. 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 in accordance with CTD table 2.7.3.1).

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

3.3.1. Clinical pharmacology

3.3.1.1. Pharmacokinetics

Absorption

Distribution

Elimination

Dose proportionality and time dependencies

Special populations

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
PK Trials			

Pharmacokinetic interaction studies

Pharmacokinetics using human biomaterials

3.3.1.2. Pharmacodynamics

Mechanism of action

Primary and Secondary pharmacology

3.3.2. 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.).

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.*

For biosimilars: The above is not applicable. Discuss the adequacy of methods (assays) and trial design used for analysis with particular attention to selection of dose and protein correction, if applicable. Discuss the results of the PK and/or PD comparability study(ies) obtained against the chosen reference medicinal product also taking into consideration prior pharmacologic knowledge of the product. Discuss the sensitivity of the endpoints and model used to detect potential product-related differences as well as the margins chosen for the comparison. When applicable, discuss any potential impact of anti-drug antibodies on PK data. Discuss the PK and/or PD bridging data (e.g. when several routes of administration are proposed, when a non-EU comparator is used in some (non)clinical studies), if applicable.

3.3.3. Conclusions on clinical pharmacology

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

For biosimilars, conclude if the available PK/PD data support biosimilarity versus the EU reference product. In addition, if a non-EU comparator has been used, conclude whether it is representative of the EU reference medicinal product.

3.3.4. 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.

3.3.4.1. Dose-response studies

Dose-response studies: not applicable for biosimilars.

3.3.4.2. Main study(ies)

The results should be presented as relevant for each of the studies, which ideally should be identifiable in the text (e.g. per protocol number).

Tables are encouraged.

The relevance of each item and, the required level of detail, needs to be considered on a case-by-case basis.

Note: the Methods or Results can be reported jointly or separately for each trial (depending on the study designs and similarities).

<Title of Study>

Methods

Limit to most relevant items from the checklist below, on a case-by-case basis.

Be aware that all post-hoc analysis are considered as not-relevant, supportive but never pivotal, a meta-analysis has to be pre specified

Study Participants

Main inclusion/exclusion criteria

Treatments

Precise details of the treatments (or other type of interventions) intended for each group and how and when they were intended to be administered. Size and duration of treatment. Timing of follow up.

Describe criteria for treatment rescue

Objectives

Specific objectives and hypotheses.

Outcomes/endpoints

Clearly defined primary and key secondary outcomes

Sample size

Randomisation and blinding (masking)

Methods used to generate the random allocation sequence and to implement it, stratification criteria. Whether or not participants, those administering interventions and those assessing outcomes were aware of group assignment and if not, how the success of masking was assessed.

Statistical methods

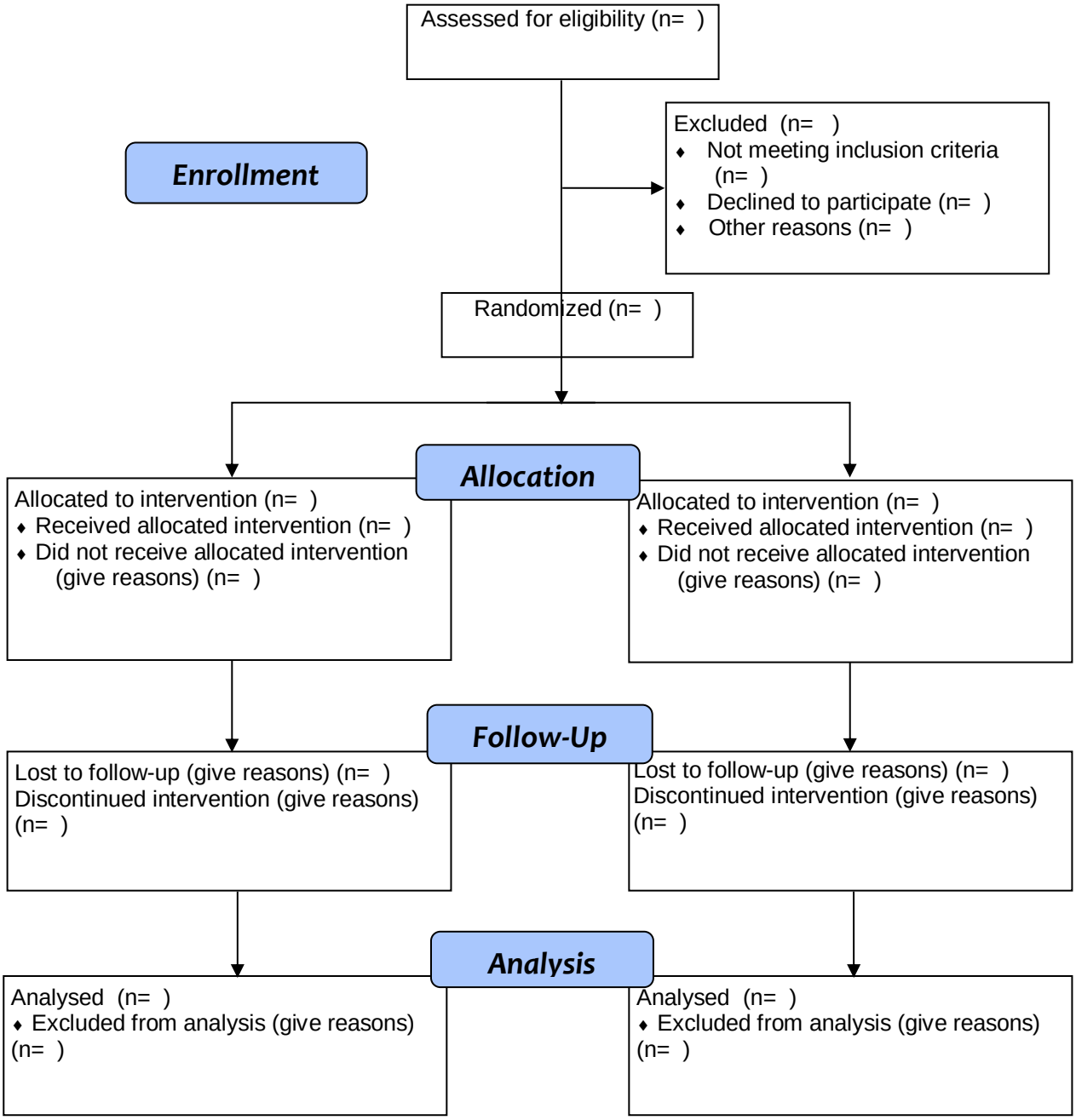
Statistical methods used to compare groups for primary outcome(s) (include definition of the populations for main analysis, error probabilities, adjustment for multiplicity, brief description of the statistical techniques used, interim analyses).

Clearly define the population used for the primary analysis.

Results

Limit to most relevant items from the checklist below, on a case-by-case basis.

Participant flow



Recruitment

Dates defining the periods of recruitment and follow-up.

Conduct of the study

State if major amendments were made to the protocol (unless described under statistical analysis). Protocol compliance and GCP inspection findings, if applicable.

Baseline data

Baseline demographic, disease and treatment characteristics by treatment group (use tables if possible).

Numbers analysed

Number of participants (denominator) in each group included in the primary and each key secondary analysis and whether the analysis was by "intention to treat". State results in absolute numbers e.g., 10/20 (50%) not just 50%. Use table if possible.

Outcomes and estimation

For each primary and secondary outcome, a summary of results for each group and estimated precision (e.g., 95% CI). Use figures and tables if possible.

Ancillary analyses

Describe any key additional analyses, such as subgroup analyses and adjusted analyses. Use figures and tables if possible.

3.3.4.3. 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.

- *Please contact the EMA product lead for a draft of this table if not already provided at submission by the Applicant.*

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".

For biosimilars, *a tabulated summary of the main clinical trial provided in support of biosimilarity should be presented.*

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><biosimilarity assessment> (see later sections).

Table 1 Summary of efficacy for trial <trial>

Title: <title> *{as indicated on the study report}*				
Study identifier	<code> *{list all codes starting with the protocol number followed by – as available - EudraCT number, ISRCT number, other codes that allow cross-referencing to publications}*			
Design	<free text> *{describe key elements of the design (cross-over, parallel, factorial, dose-escalation, fixed-dose response) including randomization, blinding, allocation concealment, mono-/multi-centre, etc.}*			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	<time> <time> <not applicable> <time> <not applicable>		
Hypothesis	<Superiority> < Equivalence> <Non-inferiority> <Exploratory: specify>			
Treatments groups *{add as many rows as needed to describe the treatment groups}*	<group descriptor> *{provide abbreviation for use later in the table of the results section}*	<treatment>. <duration>, <number randomized>		
	<group descriptor>	<treatment>. <duration>, <number randomized>		
	<group descriptor>	<treatment>. <duration>, <number randomized>		
Endpoints and definitions *{add as many rows as needed to describe the endpoints; for the secondary endpoints select the ones considered most relevant and reported in the results section}*	<Co->Primary endpoint	<label> *{generate abbreviation for use later in the table of the results section}*	<free text> *{provide brief description}*	
	<Secondary> <other: specify> endpoint	<label>	<free text> *{provide brief description}*	
	<Secondary> <other: specify> endpoint	<label>	<free text> *{provide brief description}*	
Database lock	<date>			
Results and Analysis *{present the result separate for each analysis that is considered relevant for the conclusion on the trial; in any case the pre-specified primary analysis should be presented}*				
Analysis description	**Primary Analysis**			
Analysis population and time point description	<Intent to treat> <Per protocol> <other: specify> *{consider adding a brief description of the definition of the population}* <time point>			
Descriptive statistics and estimate variability	Treatment group	<group descriptor> *{as per above terminology}*	<group descriptor> *{as per above terminology}*	<group descriptor> *{as per above terminology}*

Title: <title> *{as indicated on the study report}*				
Study identifier	<code> *{list all codes starting with the protocol number followed by – as available - EudraCT number, ISRCT number, other codes that allow cross-referencing to publications}*			
	Number of subject	<n>	<n>	<n>
	<endpoint> *{label as above}* (<statistic>) *{e.g. mean, median, etc}*	<point estimate>	<point estimate>	<point estimate>
	<variability statistic> *{e.g. standard deviation, confidence interval, etc}*	<variability>	<variability>	<variability>
	<endpoint> (<statistic>)	<point estimate>	<point estimate>	<point estimate>
	<variability statistic>	<variability>	<variability>	<variability>
	<endpoint> (<statistic>) <variability statistic>	<point estimate> <variability>	<point estimate> <variability>	<point estimate> <variability>
Effect estimate per comparison *{add as many rows as needed to describe the relevant statistical testing performed}*	<Co->Primary endpoint	Comparison groups	<group descriptors> *{as per above terminology}*	
		<test statistic> *{e.g. difference between groups}*	<point estimate>	
		<variability statistic> *{e.g. confidence interval, etc}*	<variability>	
		P-value*{indicate statistical test used, e.g. ANOVA}*	<P-value>	
	<<Co->Primary ><Secondary><other: specify> endpoint *{indicate endpoint using terminology as per row "Endpoint and definitions}*	Comparison groups	<group descriptors>	
		<test statistic>	<point estimate>	
		<variability statistic>	<variability>	
		P-value	<P-value>	
	<<Co->Primary ><Secondary><other: specify> endpoint	Comparison groups	<group descriptors>	
		<test statistic>	<point estimate>	

Title: <title> *{as indicated on the study report}*			
Study identifier	<code> *{list all codes starting with the protocol number followed by – as available - EudraCT number, ISRCT number, other codes that allow cross-referencing to publications}*		
		<variability statistic>	<variability>
		P-value	<P-value>
Notes	<free text> *{consider amongst others the following information:* *- reasons for drop-outs* *critical findings with regard to the analysis}*		
Analysis description	**<Secondary analysis> <Co-primary Analysis> <Other, specify: >** *{also indicate if the conduct of the analysis was pre-specified}*		
{repeat all the above sections for each analysis that is considered relevant}			

3.3.4.4. Clinical studies in special populations

Not applicable for biosimilars.

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.

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

3.3.4.5. In vitro biomarker test for patient selection for efficacy

Describe if applicable or state "Not applicable".

3.3.4.6. Analysis performed across trials (pooled analyses and meta-analysis)

Describe if applicable or state "Not applicable".

3.3.4.7. Supportive study(ies)

Describe if applicable or state "Not applicable".

3.3.5. 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).

Do not repeat methods and results extensively unless there are specific aspects that require discussion.

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*

Describe uncertainties by mentioning what is the source of the uncertainty (e.g., missing data), what is the item that you are uncertain about (e.g., efficacy in a subgroup) and what are the possible coping strategies if possible (e.g., submit further data to reduce uncertainty; acknowledge through labelling changes; seek expert input). Key uncertainties that cannot be resolved should be described also under the benefit-risk assessment.

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?*

For biosimilars, discuss the sensitivity of the endpoints and model used to detect differences as well as the margins chosen for the comparison.

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?*
- *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.*

For biosimilars, discuss the results of the efficacy comparability study obtained against the chosen reference medicinal product, if applicable. Consider also available experience with the reference product for plausibility of results. Discuss if there are differences observed at quality (e.g. molecular structure, glycosylation profile, formulation), non-clinical level (e.g. target receptor binding, functional activity) or PK/PD level that could affect clinical efficacy. Discuss whether pre-existing or treatment-emergent anti-drug antibodies could have an impact on efficacy, also considering the relevance for potential extrapolation to other indications of the reference product.

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

<Additional expert consultation>

<Assessment of paediatric data on clinical efficacy>

<Additional efficacy data needed in the context of a <conditional> MA <under exceptional circumstances>

The recommendation to grant a marketing authorisation under exceptional circumstances by the CHMP should carefully be considered for situations where, for a number of reasons, it does not seem possible to ever assemble a "full" dossier. Notably, a marketing authorisation under exceptional circumstances will normally remain under exceptional circumstances and not lead to a conversion into a normal marketing authorisation.

Describe here the missing data in Module 5, why it is missing (rarity of disease = exceptional, early development = conditional) and how the gap is foreseen to be bridged, i.e. which data is required to be

submitted. Alignment with discussion in section 5.7.3 on comprehensiveness of clinical data submitted in the marketing authorisation application should be taken into consideration to justify the need for additional efficacy data.

3.3.6. Conclusions on clinical efficacy

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

For biosimilars, conclude if the submitted efficacy data support biosimilarity.

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

<The following measures are necessary to address the missing efficacy data in the context of a <conditional> MA <under exceptional circumstances>:>

3.3.7. Clinical safety

3.3.7.1. Patient exposure

3.3.7.2. Adverse events

3.3.7.3. Serious adverse events, deaths, and other significant events

3.3.7.4. Laboratory findings

3.3.7.5. In vitro biomarker test for patient selection for safety

3.3.7.6. Safety in special populations

Section not applicable for biosimilars.

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.

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

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.

3.3.7.7. Immunological events

Include a short description of the bioanalytical methods, ADAs in clinical samples of HVs and patients, impact of ADAs on PK, impact of ADAs on efficacy and safety including hypersensitivity reactions (injection site reactions also by ADA status), etc.

Alternatively this information could be presented in the related sections (PK, efficacy and safety) with cross references. For biosimilars, it is preferable to present all data related to immunogenicity in the same section and cross refer as needed.

3.3.7.8. Safety related to drug-drug interactions and other interactions

Not applicable for biosimilars.

3.3.7.9. Discontinuation due to adverse events

3.3.7.10. Post marketing experience

3.3.8. 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 biosimilars:

- *Discuss the results of the comparison of the most important adverse drug reactions (type, severity and frequency). Describe the safety concerns that have been observed or that are otherwise of concern even if (yet) unobserved for the biosimilar candidate. If no confirmatory clinical study has been conducted, discuss the available data from which a similar safety profile could be inferred. Compare the immunogenicity profile of the biosimilar candidate and the reference product. If no human immunogenicity data have been generated, discuss the available data from which a similar immunogenicity profile could be inferred.*
- *Discuss available data questioning biosimilarity (e.g. differences observed at quality, non-clinical level) which could have an impact on safety/immunogenicity and/or differences observed at clinical level such as higher incidence of certain adverse events, new signal or new adverse events that were not observed for the reference product. Discuss any specific risks anticipated for the biosimilar e.g. possible safety concerns that may result from a manufacturing process different from that of the reference product, especially those related to infusion-related reactions and immunogenicity.*

<Additional expert consultation>

<Assessment of paediatric data on clinical safety>

<Additional safety data needed in the context of a <conditional> MA <under exceptional circumstances>>

The recommendation to grant a marketing authorisation under exceptional circumstances by the CHMP should carefully be considered for situations

where, for a number of reasons, it does not seem possible to ever assemble a "full" dossier. Notably, a marketing authorisation under exceptional circumstances will normally remain under exceptional circumstances and not lead to a conversion into a normal marketing authorisation.

Describe here the missing data in Module 5, why it is missing (rarity of disease = exceptional, early development = conditional) and how the gap is foreseen to be bridged, i.e. which data is required to be submitted. Alignment with discussion in section 5.7.3 on comprehensiveness of clinical data submitted in the marketing authorisation application should be taken into consideration to justify the need for additional safety data.

3.3.9. 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). For biosimilars, conclude if the submitted safety data support biosimilarity.

[Apart from the overall conclusion on safety, comment also on which safety findings should be considered for inclusion in the safety specification of the RMP (See further below).]

In case conditions for Annex II in relation to the <conditional> MA <under exceptional circumstances> have been identified, use the following statement:

<The following measures are necessary to address the missing safety data in the context of a <conditional> MA <under exceptional circumstances>:>

3.4. Risk management plan

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

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

For biosimilars and fixed combination products without new active substance, the RMP(s) of the reference/combined product(s) should be followed and cases of divergence (if any) need to be discussed and highlighted.

3.4.1. Safety Specification

Summary of safety concerns

*[**To be filled in by the CHMP/CAT Rapporteur at D80** and updated in subsequent D120 document considering all the comments]*

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

Table SVIII.1: Summary of safety concerns

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

3.4.1.1. Discussion on safety specification

*[**Complete this section at D80:** Please merge the comments with regard to the non-clinical and clinical safety concerns and specifically address the need to modify the proposed summary of safety concerns in the RMP.*

Please flag to the PRAC Rapporteur any particular issues and concerns that were identified during the assessment of the dossier that could impact the planning aspects of the Risk Management Plan; i.e. the pharmacovigilance plan or the risk minimisation measures.

***At D120, this section should be updated** considering all comments (from the CHMP/CAT Co-Rapporteur, the PRAC rapporteur, Member States, EMA…)]*

3.4.1.2. Conclusions on the safety specification

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

Having considered the data in the safety specification

<It is agreed that the safety concerns listed by the applicant are appropriate>

or

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

<It is considered that> <should also be <a> safety concern(s)>

<It is considered that the following should not be <a> safety concern(s)>

[If the second option is chosen, the issues to be addressed must be included in the LOQ]

3.4.2. Pharmacovigilance plan

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

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

[Prior to circulation of the Draft D120 LOQ, copy here the tables *found in section III.3 Summary Table of additional Pharmacovigilance activities of the RMP of the applicant and include discussion taking into account comments from PRAC, MSs, EMA etc.]*

Comment on whether routine pharmacovigilance is sufficient or whether additional activities are warranted. Comment on whether proposed activity(ies) is(are) appropriate and proportionate to the importance of the risk proposed to be addressed and if additional activities are required.]

3.4.3. Risk minimisation measures

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

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

[***Prior to circulation of the Draft D120 LOQ*** copy here the table from section V.3 Summary of risk minimisation measures of the RMP of the applicant and include discussion taking into account comments from PRAC, MSs, EMA etc..]

Comment on whether risk minimisation activities as proposed by the applicant are sufficient or whether additional risk minimisation measures are needed.]

3.4.4. Conclusion on the RMP

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

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

[A) If the RMP is acceptable:

The CHMP and PRAC considered that the risk management plan version <X> is acceptable. <In addition, minor revisions were recommended to be taken into account with the next RMP update>.

[B) If the RMP could be acceptable with revisions required before opinion.

The CHMP and PRAC considered that the risk management plan version <X> could be acceptable if the applicant implements the changes to the RMP as detailed in the endorsed Rapporteur assessment report and in the list of questions in section 6.3.

[C) If the RMP is not acceptable.]

The CHMP and PRAC considered that the risk management plan version <X> is not acceptable. Details are provided in the endorsed Rapporteur assessment report and in the list of questions in section 6.3.

3.5. Pharmacovigilance

3.5.1. Pharmacovigilance system

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

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

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

3.5.2. Periodic Safety Update Reports submission requirements

[This section should be completed by the PRAC Rapporteur prior to D120]

[For all medicinal products, except EU-M4all products, use one of the following options]

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

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

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

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

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

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

- *[In case a separate entry is needed, in addition to the already existing one, complete the following statement, providing the rationale for such addition of entry and request the applicant to clarify whether they wish to align the EBD to IBD in the list of question]*

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

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

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

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

[For EU-M4all products, use the following statement]

The first periodic safety update report should cover the six-month period following the initial scientific opinion for this product on <*date of initial scientific opinion*>.

Subsequently, the scientific opinion holder shall submit periodic safety update reports for this product every <*frequency*> until otherwise agreed.

4. <Non-Conformity with agreed Paediatric Investigation Plan>

Only in case the CHMP denies conformity with the agreed PIP, whereas the compliance check performed by the PDCO was positive, add the following sentence (this may be 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)).

< <Study(ies) identifier> <is><are> not in conformity with the agreed Paediatric Investigation Plan *[insert relevant PIP decision number(s)] as set out in Article 24 of Regulation (EC) No 1901/2006]*. The detailed grounds for the non-conformity conclusion are as follows:

- {*a detailed justification should be provided*}.>

5. Benefit risk assessment

COMMENTS
Note: The checklists used in this section (for example "☐ State the claimed indication…") and comment boxes are provided for guidance during drafting of the report – please delete the checklists and comment boxes from the final report.

Section '5. Benefit risk assessment' not applicable for biosimilar. Please replace this section by the section called 'biosimilarity assessment' (see further below)

5.1. Therapeutic Context

5.1.1. Disease or condition

- *State the claimed indication. If appropriate, shortly describe key aspects (if any) of the disease or condition studied that are important for the benefit-risk assessment (e.g., definitions).*
- *Describe the aims of therapy (e.g., to prolong survival) and key (efficacy) endpoints, if appropriate.*

The purpose of this section is to briefly mention the indication and key definitions as described in more detail in section 2.1. A clear statement is important in order to frame the benefit-risk assessment precisely.

5.1.2. Available therapies and unmet medical need

- *Shortly summarise the main available treatment options and the unmet need, if any (a detailed description is in section 2.1 Problem statement).*

The purpose of this section is to briefly mention key aspects about the unmet medical need (e.g., severity of condition, life-threatening or not, affected population) of the indication as described in more detail in section 2.1. The repetition of these key aspects is important in order to frame the benefit-risk assessment precisely and to further justify the risk attitude.

5.1.3. Main clinical studies

- *Briefly describe the design of the main trial(s) and the selected population(s).*

Comments
• Describe aspects of the condition that are most relevant for the target population and the product and thus could be considered relevant key effects to evaluate in the studies. (For instance, for a product intended to prolong survival, describe mortality.) • The unmet medical need should be described in precise epidemiological terms (e.g., incidence, mortality) as much as possible. Societal or public health implications of the

Comments

condition (e.g., impact of poor control and prevention of an infectious disease) should also be addressed where relevant.

- The main clinical trials should be described with respect to randomisation, blinding, control, dosing and study size.
- Describe these key aspects only briefly. These will already have been described in detail in the respective sections.

Hypothetical example *[delete from final report]*

5.1. Therapeutic context

5.1.1. Disease or condition

The target indication applied for by the Applicant is for the treatment of adult patients with relapsed/refractory multiple myeloma (MM). The definitions of relapsed and refractory are those of the International Myeloma Working Group (IMWG).

The aim of new treatments is to prolong progression-free survival and overall-survival, or to improve symptoms, whilst minimising toxicity.

5.1.2. Available therapies and unmet medical need

For the treatment of relapsed/refractory MM, conventional-dose chemotherapy and high-dose chemotherapy with stem cell support remain the current standard of care, along with supportive care including biophosphonates (Palumbo, 2008b). Despite progress in its current treatment and management, MM remains incurable. Patients whose disease is relapsed/refractory after treatment with conventional agents have limited treatment options and short median survival of about 9 months (Kumar, 2012).

5.1.3. Main clinical studies

The main evidence of efficacy submitted is a single phase III multicenter, randomized, open-label study comparing pomalidomide plus low-dose dexamethasone (n=302) vs. high-dose dexamethasone (n=153) in previously treated adult patients with relapsed/refractory multiple myeloma who had received at least two prior treatment regimens, including both lenalidomide and bortezomib, and had demonstrated disease progression on the last therapy.

Hypothetical example – Biosimilar *[delete from final report]*

5.1. Therapeutic Context

5.1.1 Disease or condition

[X] has been developed as a biosimilar infliximab using Remicade as a reference product and is intended to be used in the same indications as the reference product.

Hypothetical example – Biosimilar *[delete from final report]*

5.1.2 Main studies

The quality comparability exercise included comprehensive and state-of-the-art characterisation covering all relevant structural, physicochemical and biological features of infliximab. The non-clinical programme included a series of in vitro studies, an in vivo efficacy study, single and repeat dose pharmacokinetic studies in rats and a Tg197 mouse model of arthritis.

The clinical development consisted in one single dose PK study in healthy volunteers comparing three formulations of infliximab (X, EU sourced Remicade and US sourced Remicade) and one main clinical study in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy (N=450). The main study was a randomised, double-blind, parallel group, multicentre clinical study to evaluate the efficacy, safety, pharmacokinetics and immunogenicity of X compared to EU Remicade.

5.2. Favourable effects

- *State the key favourable effects (i.e., primary endpoint and secondary endpoints of clinical relevance) and shortly describe them (e.g., point estimates, confidence intervals).*
- *Consider describing key effects in important subgroups (e.g. as defined by age, sex, ethnicity, organ function, disease severity, or genetic polymorphism).*
- *Consider describing also consistency of findings between the studies and prior knowledge (if not consistent, this should be mentioned in section 5.3 as an uncertainty) and robustness of the data.*

COMMENTS

- Strive for clarity, e.g., a difference in median overall survival of 6.8 months was observed for treatment X compared to treatment Y, HR=0.8 (95% C.I.: 0.6, 0.9; logrank *P*=.001).
- Avoid interpretation and value judgements (e.g., it was convincingly shown that overall survival was greatly improved for treatment X).
- This section should be consistent with the favourable effects described in 5.6. Effects Table and with the SmPC section 5.1. No new results should be introduced here that have not been described in detail in the previous sections.
- This section does not need to be updated during the procedure unless new key results are submitted.

What are the favourable effects?

The purpose of this section is to describe in factual terms the key beneficial effects (often referred to as "benefit(s)" or "clinical benefit(s)") associated with the drug for the target population. Favourable effects are not limited to efficacy (for example, a reduction in toxicity could also be a favourable effect). Sometimes the same effect (e.g., a toxicity) can be described as a favourable effect (when that toxicity is low and this is the aim of the new therapy) or as unfavourable one (toxicity is high). In practice it does not matter if an effect is classified as favourable or unfavourable, long as it is not described twice.

What are "Key" Favourable Effects?

An important aspect to consider when deciding which of the available study outcomes to describe in the benefit-risk assessment is the need to be complete without being overly detailed. 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). Although this strategy will work in most situations, there will be more complex situations when the choice of the key effects will require deeper reflection. In such cases, the primary endpoint of the main study may not be the most important effect and in that case, secondary endpoints (or, if the study has not been adequately designed, endpoints that have not been measured in the study) could take priority.

About redundancy ("Double-Counting")

Redundancy can occur in a number of situations such as when describing correlated endpoints (e.g., when the surrogate endpoint and the true endpoint are both included), when using different response-variables based on slightly different cut-offs or time-point, or when describing the effect within a broader group and a subgroup contained in it. In principle, this type of redundancy should be avoided as it may over-emphasize certain effects.

5.3. Uncertainties and limitations about favourable effects

- *Describe any important uncertainties and limitations about the knowledge of favourable effects that is important for the benefit-risk balance, including issues with regard to the robustness of the results.*
- *This section should be updated during the procedure. If there are no remaining uncertainties and limitations that have an impact on the benefit-risk balance, this section can be completed with "There are no remaining uncertainties and limitations that have an impact on the benefit-risk balance (see section 5.7. Benefit-risk assessment and discussion)."*

COMMENTS

- Focus on important uncertainties that have an impact in terms of benefit-risk assessment. The description should be factual and value judgements should be avoided.
- Value judgments about the confidence in the decision, the impact of uncertainties on the benefit-risk balance and any actions (e.g., restriction of indication) should be described under section 5.7.1. Importance of favourable and unfavourable effects and 5.7.2. .
- Minor uncertainties on favourable effects that do not have an impact on the benefit-risk assessment and that can easily be managed (e.g., product information) will have been described in detail in previous sections (including 3.2.6. Discussion on non-clinical aspects, 0Discussion on clinical efficacy, 3.3.8. Discussion on clinical safety) and do not need to be repeated here. If still considered worth mentioning, briefly state the uncertainty and how it will be managed.
- Examples of uncertainties and limitations;
    - Indeterminate estimates, e.g., too small sample size, too broad confidence intervals, insufficient significance, withdrawal patterns that may impact on the interpretation of the results
    - Statistical aspects e.g. appropriateness of statistical model, validity of assumptions, considerations, combined analyses, missing data, imputation methods, multiplicity;
    - Assay sensitivity issues (non-inferiority / equivalence trials; treatment compliance);
    - Representativeness of the patient population expected to be treated with the product (external validity)
    - The chosen "key" effects are different from the aims of therapy described in 5.1. Therapeutic Context;
    - Positive findings on primary efficacy endpoint(s) are not supported by at least favourable trends in specified secondary efficacy measures; single pivotal trial;
    - GCP compliance issues;
    - The product used in clinical trials is not appropriately representative of the product proposed for marketing;
    - Any specific aspects of formulation (composition or development) which impact the safe and effective use of the product;
    - Inconsistency of findings between the studies and prior knowledge.
    - Inconsistent findings in important subgroups (e.g. age, gender, disease characteristics, and concomitant treatment); differences between regions (EU vs. non-EU);
- If relevant, 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).

Hypothetical example ***[delete in final report]***

5.2. Favourable effects

The HR for OS (secondary endpoint) was 0.53 (95% CI: 0.37–0.74; logrank *P*-value <.001) in favour of POM+LoDEX v. HiDEX. Median progression-free survival (primary endpoint) was 15.7 weeks v. 8.0 weeks for POM+LoDEX v. HiDEX (HR=0.45; 95% CI=0.35–0.59; logrank *P*<0.001)

5.3. Uncertainties and limitations about favourable effects

Median OS has not been evaluable yet and for a high proportion of patients the duration of survival was not known at the time of analysis (75% and 62% of randomized patients, respectively), thus there are limitations as to the maturity of the data.

5.4. Unfavourable effects

Definition of an "Unfavourable Effect"

The purpose of this section is to describe in factual terms the key unfavourable 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 or public health.

Unfavourable effects are not necessarily limited to clinical safety endpoints. For example, unfavourable effects may also be loss of efficacy on some important efficacy endpoints or other undesirable effect. Also, consider pharmacokinetic and pharmacodynamics interactions, specific non-clinical and quality aspects, important unfavourable effects in terms of public health or the environment especially for Genetically Modified Organism (GMOs); potential for abuse and misuse, which could qualify as unfavourable effects.

What are "Key" Unfavourable Effects?

An important aspect to consider when deciding which of the effects to describe is the need to be complete without being overly detailed. In practice, this can often be achieved by including the main unfavourable effects, consistent with the important (and in some cases, potential) identified risks included in the Risk Management Plan.

Try to avoid long lists of individual side-effects. Where meaningful, try to group them in terms of consequences, e.g., grouping all side-effects by severity using agreed criteria.

Note that the most important unfavourable effects are not necessarily the most common ones. Use sub-headings (or bold font) when necessary to improve clarity. Do not repeat results extensively, these are described in detail elsewhere in the report.

How to describe Unfavourable Effects?

Once key unfavourable effects have been identified, these should be described using free text. Below is a list of items to be considered on

a case-by-case to describe key unfavourable effects in quantitative and qualitative terms. Not all aspects need to be described for every unfavourable effect, only the most relevant ones.

Quantitatively	
Summarize the most important unfavourable effect in terms of	Duration, severity and frequency and reversibility (absolute end relative v.s. drugs comparator, standard of care or individuals other than those who will receive the drug)
	Relative safety, compared to standard of care, or drugs of the same pharmacological class
	Discontinuation of treatment
	Important subgroups (age, sex, ethnicity, organ function, disease severity etc.)
Qualitatively	
Describe unfavourable effect in terms of	Mechanism of action
	Relative safety, compare the toxicity profile to standard of care, or drugs of the same pharmacological class
	Type of effects (subjective, idiosyncratic, laboratory…)
	Dose-response relationship
	Severity in relation to the disease being treated
	Is this an adverse reaction that is not typical of drugs in the same class?
	Ability to predict, monitor, treat and prevent risk
	Public health and environmental risk associated with the unfavourable effect

- *State the key unfavourable effects and shortly describe them (e.g., incidence, severity, duration, reversibility, dose-response relationship; incidence of adverse events leading to withdrawals and/or hospitalisations).*
- *Consider describing key unfavourable effects in important subgroups (e.g. as defined by age, sex, ethnicity, organ function, disease severity, or genetic polymorphism).*

COMMENTS

- Strive for clarity (e.g., treatment X was associated with Grade 1-2 toxicity in 95% of patients);
- Avoid interpretation and value judgements (e.g., low-grade toxicity for treatment X was significant);
- This section should be consistent with the unfavourable effects described in 5.6. Effects Table the important identified risks described in section 3.4. Risk management plan, and the SmPC Section 4.8. No new results should be introduced here that have not been described in detail in the previous sections (typically under Clinical Aspects).
- This section does not need to be updated during the procedure unless new key results are submitted

5.5. Uncertainties and limitations about unfavourable effects

- *Describe any important uncertainties and limitations about the knowledge of unfavourable effects that is important for the benefit-risk balance.*

- *This section should be updated during the procedure. If there are no remaining limitations and uncertainties that have an impact on the benefit-risk balance, this section can be completed with "There are no remaining limitations and uncertainties that have an impact on the benefit-risk balance (see section 5.7. Benefit-risk assessment and discussion)."*

COMMENTS

- Focus on important uncertainties that have an impact in terms of benefit-risk assessment. The description should be factual.
- Value judgments about the confidence in the decision, the impact of uncertainties on the benefit-risk balance and any actions (e.g., restriction of indication) should be described under 5.7.1. Importance of favourable and unfavourable effects and 5.7.2. Balance of benefits and risks.
- Minor uncertainties that do not have an impact on the benefit-risk assessment and that can easily be managed (e.g., product information) will have been described in detail in previous sections.
- Discussion on clinical efficacy and Discussion on clinical safety do not need to be repeated here. If still considered worth mentioning, briefly state the uncertainty and how it will be managed.

Below is a non-exhaustive list of common sources of uncertainty about unfavourable effects.

Describe the adequacy/limitations of the database in terms of	Sample size
	Study design
	Duration of follow-up
	Size of key (sub) populations
	Important quality issues
	Non-clinical safety findings
	Dosing
	Type of control group
	The possibility to generalize to clinical practice
	Missing data
	Discontinuation of treatment
	Adequacy of monitoring

5.6. Effects Table

The Effects Table should be used for initial applications of new active substances (excluding biosimilars), for EU-M4all applications and for important extension of indication applications.

Initially, the Effects Table 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 Effects Table should reflect such changes. The final Effects Table should

reflect the final indication and mention only the data and uncertainties relevant to the approved target population.

- *Effect column: Provides an acronym or very short identifier of the effect (e.g. RR for response rate). The purpose is to provide a short identifier that will be familiar to readers that are experts in the field. As the Effects Table 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. Where possible, the degree of statistical uncertainty should be quantified by providing standard errors or confidence intervals.*
- *Description column: Provides a very short definition of the effect (e.g., if the effect is overall survival, OS, this could be "duration of survival from randomisation to death regardless of cause). Make sure complex acronyms or specific tools are explained (the purpose is that a reader not thoroughly familiar with the therapeutic area can quickly understand what is the effect being described). If needed, further description is included in the footnotes (e.g. by a reference to the literature).*
- *Unit column: Provide the unit of measurement for each effect (e.g., mmHg, months, %). The purpose is to provide clear description of the estimates in the subsequent columns.*
- *Treatment group columns: Summarize the key effects of the index drug driving the benefit-risk discussion. The purpose is to provide a clear and concise comparative display. Separate column(s) is (are) included for each treatment 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. The column headers ("Treatment", "Control") can be modified with the name or acronym of the different drugs (and columns can be added as appropriate). If external (historical controls) are used these should be entered in the appropriate column.*
- *Strength of evidence/Uncertainties column: Briefly describes the strength of evidence and any major uncertainty or limitation for each effect. The purpose is to at least briefly mention the strengths and weaknesses described above so that the treatment estimates are not misunderstood.*
- *References column (optional): This column has multiple purposes. 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. This is important to*

avoid over-simplification in case the table is read outside the context of the assessment report. This column can also be used to refer to specific sources of data (e.g., the acronym of a study in case of evidence from multiple studies or publications).

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

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Unfavourable Effects						

Abbreviations:
Notes:

COMMENTS

- The Effects Table is entirely based on the assessment of the key favourable and unfavourable effects, strength of evidence, limitations and uncertainties described in the previous sections. As such, there is no new element in the table that has not been described elsewhere.
- Ensure consistency between the table and the favourable, unfavourable effects and strength of evidence, uncertainties and limitations described above.
- The Effects Table should not replace the textual description of effects in the respective sections (some degree of redundancy is expected) although some numerical details can appear in the table only.

How To Describe Multiple Studies

The ET should provide as much as possible integrated ("pooled") data, when it is meaningful to do so, in order to ease communication. A reiteration of reams of data from individual studies addressing exactly the same questions is generally less informative.

In case of multiple 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 Reference column or footnotes (see also Hypothetical example of section 2.1). Effects from supportive studies can similarly be described under strength of evidence and needn't be mentioned as separate point estimates.

When meaningful (the studies are comparable in terms of design and importance), 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 or meta-analysis).

Hypothetical example [to be deleted in final report]

A hypothetical 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 January 2-10-April 2011).

Effect	Description	U	LIX	PBO	EXE	Uncertainties/ Strength of evidence	References
Favourable Effects							
HbA1c	Mean change in HbA1c from baseline	%	-0.79 (1) (-0.95,-0.63)	-0.19 (1) (-0.43,0.05)		The effect of lixisenatide was more pronounced in Asian patients compared to Caucasian patients. The lower effect in Caucasians is partly explained by a large placebo effect especially in some geographical regions.	(1)
			-0.83 (2) (-0.91, -0.75)	-0.39 (2) (-0.51, -0.28)			(2)
			-0.79 (3) (-0.89, -0.68)		-0.96 (3) (-1.06,-0.86)		(3)
			-0.82 (4) (-0.91, -0.73)	-0.10 (4) (-0.24, 0.04)			(4)
Body weight	Mean change in body weight from baseline	kg	-1.94 (1) (-2.40,-1.48)	-1.98 (1) (-2.65,-1.31)			(1)
			-2.12 (3) (-2.42, -1.82)	-1.64 (2) (-2.07,-1.20)			(2), (3)
			-2.19 (3) (-2.47, -1.91)		-3.98 (3) (-4.43,-3.53)		(3)
			-2.87 (4) (-3.26, -2.48)	-0.93 (4) (-1.39,-0.47)			
Unfavourable Effects							

Hypothetical example [to be deleted in final report]

Nausea	Incidence of nausea	%	26.9 (5)	7.3 (5)		Approximately 70-80% of the patients experiencing nausea or vomiting completed the treatment.	(5)
Vomiting	Incidence of vomiting	%	11.4 (5)	2.7 (5)			(5)
Diarrhoea	Incidence of diarrhoea	%	11.1 (5)	8.0 (5)			(5)
Hypo-glycaemia	Incidence of hypo-glycaemia	%	1.7 (1)	1.6 (1)		Hypoglycaemia is mainly seen when lixisentatide treatment is combined with sulfonylurea.	(1)
			7.0 (2)	4.8 (2)			(2)
			2.5 (3)		7.9 (3)		(3)
			22.7 (4)	15.2 (4)			(4)
ISRs	Incidence of ISRs	%	5.3 (5)	1.9 (5)			(5)
Allergic reactions	Incidence of allergic reactions	%	0.4 (5)	<0.1 (5)			(5)
Palpitations	Incidence of palpitations	%	1.5 (5)	0.7 (5)		The slightly increased incidence of palpitations and tachycardia compared to placebo indicate a propensity of lixisenatide to increase heart rate. The total number of CV events did however not differ significantly between lixisenatide and placebo (HR 1.25, 95% confidence interval 0.67-2.35).	(5)
Tachycardia	Incidence of tachycardia	%	0.7 (5)	<0.1 (5)			(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.

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

- *Discuss the importance (typically in terms of clinical relevance) of the favourable effects observed (as described above) in relation to the target disease and target population and the unmet medical need. Which effects are the most important ones given the objectives of therapy in this disease? What magnitude of the effect can be considered as meaningful and how do the observed effects compare to this?*

- *If effects are measured in terms of surrogate endpoint(s), discuss what could be the expected outcome and importance in terms of the true clinical endpoint(s).*
- *Discuss the impact of uncertainties and limitations of the data (as described above) on the importance of the favourable effects. E.g., if the true magnitude of the treatment effect could potentially be smaller than estimated due to identified uncertainties, how does this affect the clinical relevance of the effect?*
- *Discuss the importance of the unfavourable effects with respect to severity, reversibility, if they led to treatment withdrawals or not. How will the unfavourable effects impact on patient´s quality of life?*
- *Discuss the impact of uncertainties and limitations of the data (as described above) on the importance of the unfavourable effects.*
- *If relevant, discuss if the importance of favourable and unfavourable effects differ between subgroups of the proposed target population.*

Comments

- Whereas previous sections mainly focus on description of the data, this section focuses on interpretation of the data, typically using value judgments about the importance of the observed effects and associated uncertainties and limitations of the data.
- In this section quantitative data and study descriptions do not need to be repeated. Instead, use value judgement to interpret the importance of the effects and the impact of any associated uncertainties and limitations of the data described in earlier sections.

The purpose of this section is to describe using value judgments the importance of the effects and the impact of uncertainties described above. When the benefit-risk balance is not self-evident, this section will be central to the whole benefit-risk assessment. Thus this section has to be worded carefully, aiming to explain and justify as well as possible the value judgments.

To describe the value judgments, a general approach is to compare the importance of different effects to each other. For example, one may state that improving overall survival is the most important outcome, that an improvement in overall survival of 1 month or more is clinically relevant, and that the observed improvement from 2 to 4 months is very clinically relevant, and that a worsening of severe and life-threatening toxicity from 25% to 30% was reversible and did not

lead to treatment discontinuation or significant worsening in quality of life.

If applicable, discuss the importance of effects in certain subgroups (e.g., importance of duration of survival may be lower in a symptomatic condition an elderly individuals compared to a younger population).

Describing the impact of uncertainties and limitations

In this section, it is important to describe the impact of uncertainties and limitations on the value judgments. For instance a high uncertainty in terms of important favourable effects may generally reduce their value. Uncertainty about the drug's not being harmful may also have an impact on the importance given to safety aspects. It may also be important to highlight "strength of evidence" to rule out the existence of important uncertainty, by describing, for example, that the study was methodologically sound, that the results were consistent across statistical analyses, important subgroups, and studies, precise and unbiased estimates, or very significant p-values.

In the earlier assessments, due to many unsettled issues it may be 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.

5.7.2. Balance of benefits and risks

- *Describe the tradeoffs – do the favourable effects outweigh the unfavourable effects given the current state of knowledge, uncertainties and limitations? Explain.If applicable, discuss any actions needed to address important limitations or uncertainties, such as warnings in the product information, restriction of indication, contraindication, need for future studies (unless already described above).*

COMMENTS

- This section can be relatively short unless the impact of remaining uncertainties that have impact on the confidence in the benefit-risk balance and any limitations needs to be described in detail. Wordings like "the benefit/risk balance is **currently negative**" or "the benefit/risk balance is **currently undetermined**" may be the most adequate choice during the first phases of the assessment procedure.
- Consider explaining the reason for the proposed indication (restriction or generalisation compared to trial data; major deviations from previous wordings of the indications within the same therapeutic area). The place in therapy and duration of treatment may also warrant further discussion.

Describing trade-offs

In essence the task of describing trade-offs consists in stating the willingness to forego the achievement of one objective against the achievement of another objective (e.g., if the aims of treatment are to minimise toxicity and to improve efficacy, then the question is how much achievement on minimising toxicity is one willing to give up in order to improve achievement in terms of efficacy?)

This assessment will require subjective judgements, but expert (from literature or expert meetings) and patient input as well as previous decisions for other products in the field should be taken into account and explained, if available.

There are several approaches on how to describe the weighing of trade-offs in the benefit-risk assessment benefit. A "descriptive" approach with explicit considerations about the importance of the different effects and how trade-offs are weighed will generally be appropriate.

- *"Descriptive" approach*

This approach generally starts by defining the importance of different effects observed. Once the different effects are ranked according to their importance, value trade-offs can be described along the hierarchy of effects by stating what would be the maximum loss that one is willing to accept in terms of a certain effect in order to improve likelihood of achieving a gain on the next most important effect. These trade-offs are then considered all together to determine the balance of favourable and unfavourable effects.

- *"Basic" approach*

A more basic approach, which can be a reasonable option where high precision in the description of the weighing of trade-offs is not needed or the trade-off is self-evident, is to describe using common language the weight given to each effect in terms of e.g., clinical relevance (e.g., irrelevant, modest, slightly relevant, relevant, very relevant). In these situations, the benefits and risks can be weighed intuitively and only general statements need to be provided (e.g., "benefit-risk balance is clearly positive").

- *"Quantitative" approaches*

These methods use an explicit relative weighing of trade-offs (as for the "descriptive" approach described above), which are then combined using different types of analyses. No single method has yet emerged as optimal in its current form and more experience is needed to see what methods work best and in what situations. If any quantitative methods are considered useful for the benefit-risk assessment, the methods should be explained, and results should be summarised and discussed in this section.

- *Special situations*

There are situations when a precise weighing of trade-offs in the benefit-risk assessment is not necessary. For instance, when there are

comparative studies against a well-established and accepted golden standard, if both the efficacy and safety are similar or superior to the golden standard in terms of all the important outcomes, no trade-offs are necessary (the benefit-risk balance will by definition be positive).

Justifying the therapeutic indication

Careful justification of evidence and assumptions is critical particular in case of restriction or generalisation of the therapeutic indication in terms of patient (e.g., benefit-risk restricted to a subgroup or in an unrestricted population compared to the main clinical trials), disease (e.g., benefit-risk restricted to high-risk subgroup or unrestricted compared to the main clinical trials) or treatment characteristics (e.g., first-line v. second-line; monotherapy v. combination, compared to the main clinical trials).

Hypothetical example (annotated) ***[delete from final report]***

5.7.1. Importance of favourable and unfavourable effects

[Describe the importance:] The most important effects observed are (in order of importance), a 4 months improvement in overall survival, a 10% increase in Grade 3-4 toxicity, and a 10% increase in chronic Grade 3-4 toxicity. [Justify why these are important] A 2 month improvement in overall survival is considered the minimally clinically relevant effect worthwhile detecting. Differences in the range of 3 to 5 months are considered of great relevance to patients. Anything above 6 months would be considered a dramatic effect. [Strength of evidence:] The evidence of efficacy was considered statistically convincing and there is good concordance among efficacy endpoints. [Impact of uncertainty:] Even if in clinical practice the population might be less fit and the benefit could be slightly lower, major differences are not expected.

Traditionally 20% Grade 3-4 toxicity has been considered acceptable for treatment of advanced cancer with a median survival of 6 months and without available established treatments, provided that there was an improvement on overall survival of 2 months or more. In principle, a worsening of Grade 3-4 toxicity above 40-50% would be considered a very poor outcome and anything above this practically unacceptable. [Impact of uncertainty:] Even if in clinical practice the toxicity could be slightly higher, this is not expected to change the conclusions. Educational material and surveillance are implemented to minimise this potential risk (see RMP).

The incidence in Grade 1-2 toxicity for similar agents in this disease is generally in the order of 40%. Higher incidences have been observed and are of some clinical relevant to some patients. If this occurred in the vast majority of patients (75% or more) this would be considered a poor outcome that would require careful consideration although this would not be considered a priori unacceptable.

Hypothetical example (annotated) *[delete from final report]*

5.7.2. Balance of favourable and unfavourable effects

- Using the "Descriptive" approach

  [Weigh the tradeoffs between Grade 3-4- toxicity and survival:] Given the poor prognosis and lack of available treatments it may be possible to accept this level of toxicity but one would need to observe an effect on overall survival of at least 3 months. The effect on overall survival observed in the pivotal trials was about 4 months improvement. Given the poor long-term prognosis, the 4 months improvement over active control is considered more important than the 10% increase in toxicity and would probably be favourable even if the toxicity had been up to a 20% increase. Therefore the increase in toxicity is clearly outweighed by the substantial increase in overall survival.

  [Weigh the tradeoffs between Grade 1-2 and Grade 3-4- toxicity:] The chronic Grade 1-2 toxicity observed was also higher and around 50% compared to 40% for standard treatment. Compared to a 10% increase in Grade 3-4 toxicity, the 10% increase in Grade 1-2 toxicity is considered of even less concern. These would only constitute a similar concern if they affected the vast majority of patients (say, 75% or more) and if they were largely irreversible both of which were not the case.

  [Sum up the weights intuitively and conclude:] The 4 months improvement in overall survival outweighs the 10% increase in Grade 3-4 and chronic Grade 3-4 toxicity. With the observed effect on overall survival, even much higher toxicity would be considered acceptable, such as a worsening close to 20% in Grade 3-4 or close to 75% in Grade 3-4 toxicity. Considering all favourable and unfavourable effects, the benefit-risk balance is considered positive.

- Using the "Basic" approach

  [Sum up the weights intuitively and conclude:] The 4 month improvement in median overall survival observed was considered to be very clinically relevant from a clinical point of view, the 10% increase in grade 3-4 toxicity was considered of limited clinical relevance and the 10% increase in grade 1-2 toxicity was considered of no clinical relevance. Considering all favourable and unfavourable effects, the benefit-risk balance is considered positive.

5.7.3. Additional considerations on the benefit-risk balance

- *Discuss regulatory options for approval (standard marketing authorisation, conditional marketing authorisation, authorisation under exceptional circumstances). If applicable, elaborate on the detailed reasons (scope, requirements) for conditional approval or an approval under exceptional circumstances; in the frame of this discussion each of the following criteria should be considered and discussed when assessing whether the clinical data*

submitted in the marketing authorisation application can be considered comprehensive:

1. *Quality of evidence (including feasibility considerations)*

   Methodological strengths and weaknesses of the clinical program, with focus on pivotal trial(s). Credibility /attributability of treatment effect and safety findings (both efficacy and safety). Trial conduct and GCP (prohibitive GCP findings?). The judgment of "Quality of evidence" should include feasibility considerations.

   Which data/trial designs (e.g. RCT or SAT) can be reasonably expected based on epidemiological considerations? Are there limitations due to the rarity of disease? Is randomization feasible?

2. *Efficacy: precision of effect size*

   Precision to measure/determine effect size/quantify efficacy, biostatistical considerations.

3. *Efficacy: clinical meaningfulness of the endpoint*

   Clinical endpoint versus biomarker or endpoint with clear mechanistic link to clinical outcome measure. Biomarker could also reflect pharmacological activity but not necessarily reflect clinically relevant outcome.

4. *Efficacy: duration of efficacy*

   Maturity of efficacy follow-up in the context of disease setting and aim of treatment

5. *Safety: exposure*

   e.g. patient numbers to understand the safety profile, in the context of what can be expected based e.g. on the mechanism of action of the product and specific characteristics of the disease. Have AEs of special interest been captured?

6. *Safety: length of follow-up*

   Detection of acute, medium, long-term toxicities. Maturity of follow-up and granularity of AE/ADR detection.

7. *Target population vs study population*

   Has the target population (e.g. age, line of treatment) been covered in the trial population or is part of the indicated patient population missing? If extrapolation is used, is an explicit confirmation by data (post approval) required? Is efficacy driven by a subpopulation which is not representative of the target population?

8. *Pharmacological rationale*

Strong pharmacological rationale e.g. monogenetic disease treated by replacement of the defected gene or gene product by gene therapy or enzyme replacement therapy

9. *Natural history/ course of the disease*

   Is additional information added/included that helps in the interpretation of the data and adds context?}

Based on the above, the clinical data are <not> considered comprehensive.

- Discuss what is recommended to advance knowledge (e.g., recommended further studies, if not already described in earlier sections).
- If there are no additional considerations that apply to this benefit-risk assessment, this section can be completed with "Not applicable."

COMMENTS

- Do not repeat previous sections. In particular, do not use this section to re-state important benefits, risks, uncertainties, their impact on the decision; these should have been described in previous sections.
- Consider discussing the consistency of this benefit-risk assessment with similar past assessments, and explain any differences.
- Is the benefit-risk balance expected to be the same over the time of treatment?

<Conditional marketing authorisation>

{Discuss the elements of comprehensive data that are not available in the submission; for clinical data, a cross-reference to the above discussion is sufficient}

As comprehensive data on the product are not available <as discussed above>, a conditional marketing authorisation <was requested by the applicant in the initial submission> <is proposed subject to consultation with the applicant>.

In case a conditional marketing authorisation is supported [select text as applicable, at least one of the options must apply]:

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the <treatment> <prevention> <medical diagnosis> of a <seriously debilitating> <life-threatening> disease. In addition the product <is to be used in emergency situations in response to public health threats duly recognised by the <World Health Organisation> <EU>> <and> <is designated as an orphan medicinal product>>.

Include corresponding discussion to support life-threatening or seriously debilitating nature of the disease.

The product is considered to fulfil the requirements for a conditional marketing authorisation:

During the procedure, the (Co)Rapporteur should assess the validity of the reason(s)/data put forward by the applicant according to the guideline for conditional Marketing Authorisation pursuant to

Commission Regulation No 507/2006) and document in this section that CHMP considers that all criteria are met. This can be succinct. Additional arguments may be included where appropriate.

- The benefit-risk balance is positive, as discussed.
- It is likely that the applicant will be able to provide comprehensive data. *{Summarise the studies (and/or preclinical / quality specific obligations in emergency situations) to be conducted and why they are considered feasible}*
- Unmet medical needs will be addressed, as *{include detailed discussion why there are no satisfactory methods authorised at all, or why the product will provide major therapeutic advantage over the authorised methods. When assessment of major therapeutic advantage over existing methods is needed, avoid the expression 'significant benefit', in particular for orphan medicines as it has a distinct regulatory meaning in the context of the parallel COMP assessment of maintenance of the orphan drug designation.}*.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. *{Summarise the reasons for this conclusion}*

In case a conditional marketing authorisation is not recommended [select text as applicable, at least one of the options must apply]:

<It is considered that the product does not fall under the scope of a conditional marketing authorisation as it is not intended for the treatment, prevention or medical diagnosis of a seriously debilitating or life-threatening disease.>

<The product is not recommended for a conditional marketing authorisation as , <the benefit-risk balance is negative (as discussed)>, <the applicant is unlikely to be able to provide comprehensive data after authorisation>, <it has not been demonstrated that the product will address an unmet medical need>, <and> <the benefits to public health of the immediate availability do not outweigh the risks inherent in the fact that additional data are still required>.

All scientific arguments of the applicant should be discussed. For reasons of (a) disease not being considered life-threatening or seriously debilitating, (b) comprehensive data unlikely to be generated post-authorisation, (c) not addressing unmet medical need and (d) benefits of immediate availability not outweigh the risks, include here corresponding discussion.

<Marketing authorisation under exceptional circumstances>

{Discuss the elements of comprehensive data that are not available in the submission; for clinical data, a cross-reference to the above discussion is sufficient}

<As comprehensive data on the product are not available, a marketing authorisation under exceptional circumstances <was requested by the applicant in the initial submission> <is proposed , subject to consultation with the applicant>.>

In case a marketing authorisation under exceptional circumstances is recommended [select text as applicable, at least one of the options must apply]:

It is considered that the applicant has sufficiently demonstrated that it is not possible to provide comprehensive data on the efficacy and safety under normal conditions of use, because <the applied for indication is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence> <in the present state of scientific knowledge, comprehensive information cannot be provided> <it would be contrary to generally accepted principles of medical ethics to collect such information>. *{Include corresponding discussion on this conclusion.}* Therefore, recommending a marketing authorisation under exceptional circumstances is considered appropriate.

In case a marketing authorisation under exceptional circumstances is not recommended.

It is considered that the absence of comprehensive data cannot be addressed by considering the benefit-risk balance in the context of a marketing authorisation under exceptional circumstances, as the applicant has not sufficiently demonstrated that it is not possible to provide comprehensive data on the efficacy and safety under normal conditions of use. *{Include discussion why arguments of the applicant are not supported.>*

5.8. Conclusions

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

6. <Biosimilarity assessment>

6.1. Comparability exercise and indications claimed

State the claimed indications and if the applicant is claiming all or only part of the approved indications of the reference product.

Briefly summarise (in a few sentences) the main aspects of the comparability exercise conducted (including analytical, functional (e.g. biological activity), non-clinical, and clinical data) and whether the development plan followed respective EMA guidelines and/or CHMP advice.

6.2. Results supporting biosimilarity

Describe the results of the comparability exercise in terms of quality, non-clinical and clinical PK/PD, efficacy, safety and immunogenicity data that support a claim of biosimilarity.

6.3. Uncertainties and limitations about biosimilarity

- *Describe concerns/uncertainties with regard to biosimilarity due to observed differences in analytical, functional, non-clinical and/or clinical aspects (e.g. comparability margins not met; differences in immunogenicity or infusion-related reactions; new drug reactions or signals compared to reference product) or due to missing relevant data.*
- *This section should be updated during the procedure. If there are no remaining uncertainties and limitations that have an impact on the biosimilarity conclusion, this section can be completed with "There are no remaining uncertainties and limitations that have an impact on the conclusion of biosimilarity.*

6.4. Discussion on biosimilarity

Describe the importance of the data supporting or questioning similarity in terms of efficacy and safety.

Discuss the impact of any uncertainties or issues with the comparability exercise in terms of efficacy and safety, e.g. are the differences observed relevant and expected to have an impact on the efficacy and/or safety/immunogenicity of the biosimilar candidate in comparison to the reference product.

Describe if the comparability exercise has been successful or not and state explicitly if similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy has been established. Discuss the strength of evidence.

Successful comparability exercises (e.g., for biosimilar applications) do not require trade-offs (see general guidance) but a justification about whether the comparability exercise has been successful according to conventional scientific standards to conclude similarity in efficacy and safety.

If applicable, discuss any actions needed to address important limitations or uncertainties (e.g. post-marketing study to provide a more precise estimate of an identified risk).

6.5. Extrapolation of safety and efficacy

When clinical comparability has been shown in one indication, and the applicant is applying for several indications of the reference product, the possibility of extrapolation of a conclusion of similar safety and efficacy to the other indications should be discussed in this section, taking into account the totality of data from the comparability exercise. Discuss as appropriate quality, non-clinical, clinical data, mechanism of action, receptor(s) mediating the effects, supporting extrapolation and if comparability between the biosimilar candidate and the reference can be concluded for all claimed indications of the reference product.

6.6. Additional considerations

- *Discuss what is recommended to advance knowledge (e.g., recommended further studies, if not already described in earlier sections).*
- *If there are no additional considerations that apply, this section can be completed with "Not applicable."*
- *Discuss the potential for misuse and off label use (e.g. in case not all indications or routes of administration of the reference product are approved for the biosimilar).*

6.7. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, <name of product> is considered <not> biosimilar to <reference product>. Therefore, a benefit/risk balance comparable to the reference product <can><cannot> be concluded.

7. List of questions < to be addressed in writing <and/or in an Oral Explanation*>

*[*in case of accelerated assessment]*

[Make cross-references from the actual question to what is stated in the scientific discussion. Try to limit the "other concerns" to what is needed to know.]

Definitions of questions:

"Major objections", preclude a recommendation for marketing authorisation or the granting of an ancillary claim (new active substance status, and/or additional year of marketing protection/data exclusivity). 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.

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.

7.1. Quality aspects

Major objections

Drug substance **[related to additional data provided by applicant only]**

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

Drug substance *[***applicant's part as provided by ASMF holder***]*

Note: In case the ASMF procedure is used the following should be stated in case Major Objections are being raised on the restricted part of the ASMF:

"For Major Objections on the restricted part of the ASMF see separate Appendix on the ASMF"

Drug product

Other concerns

Drug substance *[related to additional data provided by applicant only]*

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

Drug substance *[applicant's part as provided by ASMF holder]*

Note: When applicable: "For Other Concerns on the restricted part of the ASMF see separate Appendix on the ASMF"

Drug product

7.2. Non-clinical aspects

Major objections

Pharmacology

Pharmacokinetics

Toxicology

Other concerns

Pharmacology

Pharmacokinetics

Toxicology

7.3. Clinical aspects

Major objections

Pharmacokinetics

Pharmacodynamics

Clinical efficacy

Clinical safety

Other concerns

Pharmacokinetics

Pharmacodynamics

Clinical efficacy

Clinical safety

7.4. Risk management plan

Major objections

Safety specification

Pharmacovigilance plan

Risk minimisation measures

Other concerns

Safety specification

Pharmacovigilance plan

Risk minimisation measures

Public Summary of the RMP

The Applicant should update the Part VI "Summary of activities in the risk management plan by medicinal product", in line with the issues raised in other parts of the RMP.

7.5. Pharmacovigilance

<Major objections>

<Other concerns>

7.6. <Orphan similarity and derogations>

<Major objections>

<Other concerns>

7.7. <New active substance status>

<Major objections>

<Other concerns>

7.8. <Additional data exclusivity /Marketing protection>

<Major objections>

<Other concerns>

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

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

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

8.1. Conditions for the marketing authorisation

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

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

8.2. Proposed list of post-authorisation measures

[This table should be reserved to include post-authorisation measures that are part of the marketing authorisation, such as specific obligations, Annex II conditions, additional pharmacovigilance activities (category 3 studies in the RMP)]

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

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

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

Proposed list of recommendations:

Recommendations pertain to quality, non-clinical (e.g. ERA, PK/PD, PAES if not key to the B/R).**Description of post-authorisation measure(s)**
1.
2.

8.3. Summary of product characteristics (SmPC)

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

See attached edited product information.

8.4. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004 (REG), Invented name (INN) <is included in> <is not included in> the additional monitoring list for the following reasons <include reason(s)>.

If this product is included in the additional monitoring list, the summary of product characteristics and the package leaflet includes the following statement "This medicinal product is subject to additional monitoring, this will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions", preceded by an inverted equilateral black triangle.

8.5. 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.

See attached edited product information.

8.6. Package leaflet (PL)

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

See attached edited product information.

User consultation

[For guidance please see section 10.]

[*For EU-M4all: In case a user testing was not submitted, please include the following sentence:* < A User testing of the Package Leaflet was not submitted by the applicant. This is not a mandatory requirement for a scientific opinion on a medicinal product under Article 58 of Regulation (EC) No 726/2004.>]

Conclusion from the checklist for the review of user consultation

<Quick Response (QR) code>

<The review of the QR code request submitted by the MAH is presented in a separate attachment to this report (checklist available for download here: Quick Response (QR) code). >

9. Appendices (as appropriate)

9.1. <Co>Rapporteurs><CHMP><CAT> questions on the ASM (active substance manufacturer) restricted part of the DMF

[NOTE that this annex should not be sent to the MAH but only to the holder of the DMF.]

9.2. AR on New Active Substance Claim dated < >

9.3. AR on similarity dated < >

9.4. AR on derogations dated < >

9.5. AR on the novelty of the indication/significant clinical benefit in comparison with existing therapies – Article 14(11) <date>

9.6. AR on the novelty of the indication in comparison with existing therapies and the significant non-clinical or clinical data in relation to the claimed new indication – Article 10(5) <date>

9.7. AR on the significant non-clinical or clinical data in relation to the claimed new indication – Article 74a <date>

10. QRD checklist for the review of user testing results

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

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

- *EC Readability Guideline*
  https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-2/c/2009_01_12_readability_guideline_final_en.pdf
- *"Operational procedure on Handling of "Consultation with target patient groups" on Package Leaflets (PL) for Centrally Authorised Products for Human Use*
  https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/operational-procedure-handling-consultation-target-patient-groups-package-leaflets-centrally_en.pdf
- *"Consultation with Target Patient Groups-meeting the requirements of Article 59(3) without the need for a full test-Recommendations for Bridging"*
  https://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/Consulation_PatientsGroups/CMDh_100_2007_clean.pdf
- *"Position paper on user testing of package leaflets"*
  https://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/Consulation_PatientsGroups/CMDh_234_2011_Rev01_2016_12_clean.pdf

PRODUCT INFORMATION

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

- Full user testing report provided ☐ yes ☐no

- Focus test report provided ☐ yes ☐no

- Bridging form provided[1] ☐ yes ☐no

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

- In case bridging form[1] has been provided, please perform the assessment in the bridging form and state the overall conclusion/recommendations below:

_____
_____
_____
_____
_____
_____
_____

- Is the justification for bridging acceptable? ☐ yes ☐ no

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

Reasons _____
_____
_____
_____

[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]*

_____
_____
_____
_____

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

1. Technical assessment

1.1 Recruitment

- Is the interviewed population acceptable? ☐ yes ☐ no ☐ no information

Comments/further details:

Guidance regarding Recruitment

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

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

1.2 Questionnaire

- Is the number of questions _____ sufficient? ☐ yes ☐ no ☐ no information
- Questions cover significant (safety) issues for the PL concerned? ☐ yes ☐ no ☐no information

Comments/further details:

VIII.4.2 Guidance regarding Questionnaire

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

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

- *Do the questions cover the key messages and the following areas?*
- *=>General impressions of package leaflet;*

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

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

1.3 Time aspects

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

Comments/further details:

Guidance regarding Time aspects

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

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

1.4 Procedural aspects

- Rounds of testing including pilot _____ ☐ yes ☐ no ☐ no information

Comments/further details:

Guidance regarding Procedural aspects

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

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

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

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

- *Does it makes use of modification phases in-between the testing rounds in order to maximise readability?*

- *Do interviewers use scenarios or live demonstrations (e.g. in order to increase the efficiency of the test, if appropriate.*

1.5 Interview aspects

- Was the interview conducted in well structured/organised manner? ☐ yes ☐ no ☐ no information

Comments/further details:

Guidance regarding Interview aspects

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

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

2. Evaluation of responses

2.1 Evaluation system

- Is the qualitative evaluation of responses acceptable? ☐ yes ☐ no ☐ no information

- Does the evaluation methodology satisfy the minimum prerequisites? ☐ yes ☐ no ☐ no information

Comments/further details:

Guidance regarding Evaluation system

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

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

1. *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?")*

2. *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?*

3. *If the company recorded the body language and behaviour of the participant, it should be described how it will influence the assessment/ results of the user testing.*

2.2 Question rating system

- Is the quantitative evaluation of responses acceptable? ☐ yes ☐ no ☐ no information

Comments/further details:

Guidance regarding Questions rating system

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

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

3. Data processing

- Are data well recorded and documented? ☐ yes ☐ no ☐ no information

Comments/further details:

Guidance regarding Data processing

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

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

4. Quality aspects

4.1 Evaluation of diagnostic questions

- Does the methodology follow Readability guideline Annex? ☐ yes ☐ no ☐ no information
- Overall, each and every question meets criterion of 81% correct answers (e.g. 16 out of 20 participants) ☐yes ☐ no ☐ no information

Comments/further details:

4.2 Evaluation of layout and design

- Follows general design principles of Readability guideline ☐ yes ☐ no
- Language includes patient friendly descriptions ☐ yes ☐ no

- Layout navigable ☐ yes ☐ no
- Use of diagrams acceptable ☐ yes ☐ no

Comments/further details:

Guidance regarding Quality aspects

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

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

Special focus should be given to the following elements:

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

5. Diagnostic quality/evaluation

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

Comments/further details:

Guidance regarding Diagnostic quality/evaluation

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

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

6. Conclusions

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

CONCLUSION/OVERVIEW

Guidance regarding 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?*