Guidance document for the content of the <Co-> Rapporteur day <60*><80> critical assessment report

**in case of accelerated assessment for procedures starting from September 2016 onwards*

Clinical aspects

<Invented name>

<(Active substance)>

EMEA/H/C/<xxx>

Applicant:

CHMP Rapporteur:	
CHMP Co-rapporteur:	
EMA EPL:	
EMA PM:	
Start of the procedure:	
Date of this report:	
Deadline for comments:	

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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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):	
Rapporteur contact person: **Co-Rapporteur contact person:** **EMA Product Lead:** **Procedure Manager:**	**Name:** Tel: Fax: Email: **Name:** Tel: Fax: Email: **Name:** Tel: Fax: Email: **Name:** Tel: Fax: Email:
Names of the Rapporteur assessors (internal and external):	**Quality:** **Name(s)** Tel: Fax: Email: **Non-clinical:** **Name(s)** Tel: Fax: Email: **Clinical :** **Name(s)** Tel: Fax: Email:

Names of the Co-Rapporteur assessors (internal and external):	**Quality:** **Name(s)** Tel: Fax: Email: **Non-clinical:** **Name(s)** Tel: Fax: Email: **Clinical:** **Name(s)** Tel: Fax:

Declarations

☐ The assessor confirms that proprietary information on, or reference to, third parties (e.g. ASMF holder) or products are not included in this assessment, unless there are previous contracts and/or agreements with the third party(ies).

☐ The assessor confirms that reference to ongoing assessments or development plans for other products is not included in this assessment report.

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

List of abbreviations

General Guidance

The report should be sufficiently detailed to allow for secondary assessment by other CHMP experts.

The use of tables/graphs/figures is encouraged; examples are given in the template and are to be used as appropriate. Tables taken from the dossier may also be appended to the assessment. Don't forget footnotes.

Cross-references should be used to clearly indicate the origin of any information used in the report, such as the specific parts of the dossier (e.g. overview, summary, study reports), references to the literature or other sources.

Reference to information which is confidential and should not be seen by the applicant (e.g. reference to the assessment of another medicinal product) should be clearly marked as "Confidential" and highlighted using a yellow background. These sections will be removed before the assessment is sent to the applicant.

The principle of the template is to make clear distinctions between presentation of data (Methodology and results) and the judgement ("assessor's comment").

Separate pages have been added in the template for the inclusion of a list of abbreviations and a list of references, to be completed when necessary.

It is recommended that the font used in the main text be Verdana, size 9.

See specific CHMP or CHMP/ICH Notes for guidance as a general framework for guidance:

http://www.emea.eu.int/index/indexh1.htm

Clinical critical assessment

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 and clinical study reports ("original data"), bibliographical references, a combination of the two, or if data are absent.

IMPORTANT NOTE: An update of the template/guidance has been implemented in 3Q10 with the intention to improve transparency and clarity of the report based on comments received on published EPARs. These updates include additional guidance on the discussion of e.g. design and

analyses of the main studies, as well as the introduction of a summary table of the main efficacy results. It should however be noted that

this update by no means intended to amend or extend the evidential standards and decision criteria for the regulatory assessment.

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).

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. See further guidance provided in the Overview template guidance document.

1. Introduction

1.1. Type of application and aspects on development

Type of Application:

Indicate type of marketing authorisation application (reference to the legal basis of the application; complete/abridged. (For further guidance see overview template/guidance document),

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.

Indicate if the applicant has requested accelerated assessment and the fulfilment of relevant criteria pursuant to article 14(9) of Regulation (EC) No 726/2004. See relevant CHMP guideline (EMEA/419127/05)

<The CHMP <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 should propose to revert to standard timetable:

<However, during assessment the (Co) Rapporteur concluded that it is no longer appropriate to

pursue accelerated assessment, as {include summary of reasons for reverting to *standard timetable}*.>

Exceptional circumstances and Conditional approval

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

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

- 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}*.
- 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}*

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

Biosimilarity

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

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

Aspects of development:

Comment on the clinical development programme in view of the proposed indication and posologies.

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 of development in other special populations such as in elderly, in males/females and in ethnic minorities. State the number and characteristics of healthy volunteers/patients/males/females included in the studies, as appropriate, (see further section III.1 for the inclusion of a more elaborate table which should be in accordance with CTD table 2.7.3.1 as appropriate).

CHMP guidance

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.

Drug development may have been performed considering the criteria for a conditional approval/exceptional circumstances and the assessment of the fulfilment of relevant criteria is an integrated part of this

report (see above).

- Legal basis
- Conditional approval/Approval under exceptional circumstances
- Accelerated procedure
- Biosimilar application
- CHMP guidelines/Scientific Advice

- 1 year data exclusivity
- Significance of paediatric studies

1.2. GCP aspects

GCP should be addressed here and in section III.1 and also in the "overview module" of the assessment.

In this section specifically address:

- *Any concerns raised during the assessment about compliance with GCP or related regulatory and ethical requirements (data accuracy or protocol compliance and compliance with ethical aspects).*
- *Statement on application of ethical standards in clinical trials, where appropriate (Art 8 (ia) of the amended Directive; Art 9.4(c) and Art 127 (a) of the new Regulation) "The applicant has to provide a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.", where applicable.*
- *Discuss the need for a GCP inspection.*

A GCP inspection could be requested on a triggered or random basis:

- *Implausible results (e.g. biologically unlikely conflicting results between studies or sites).*
- *Critical dependence on a single or small group of studies.*
- *Major impact factor - e.g. a vaccine to which an entire infant population might be exposed.*
- *Novel therapy.*
- *Potential for ethical concerns (vulnerable populations: paediatric, mentally impaired, lack of alternative therapy, institutionalised subjects, populations in developing world, etc.).*
- *Lack of inspection experience with geographical origin of data and/or data coming from developing countries.*
- *Sponsor not previously inspected.*

Detailed information on triggers for inspection can be found in the document "Training document on Triggers for GCP inspection" which is available from your local GCP inspectorate or EMEA inspection sector.

To request a GCP inspection:

- *Contact your local GCP inspectorate.*
- *Contact EMEA inspection sector - GCP inspection coordination.*
- *Determine with them the clinical trial(s), sites and special concerns or issues to be addressed/the trigger or random factor related to the inspection.*
- *EMEA inspection sector formulates the formal inspection request for review by the inspectors and agreement by the Rapporteur and Co-Rapporteur prior to adoption by CHMP (day 90 or 120).*

1.3. Orphan medicinal products

Indicate if, and when the product received Orphan Drug Designation related to the applied indication. State the orphan indication and the prevalence of the condition (from COMP summary report).

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

For medicinal products similar to an orphan medicinal product; elaborations on similarity and on the data supporting clinical superiority to an already authorised orphan medicinal product in the same indication (refer to Commission Regulation (EC) No 847/2000.

Article 3d: Definitions) are done in separate reports by the CHMP Rapporteurs (see Appendix in the Overview). For breaking of market exclusivity (in case of similar products), clinical superiority needs assessment (see Appendix in Overview).

Special consideration may have to be given to orphan designated products with regard to the scope of the orphan condition in relation to the therapeutic indication claimed by the applicant.

2. Clinical pharmacology

2.1. Pharmacokinetics

2.1.1. Introduction

A short background information on study design (e.g. crossover/population pharmacokinetics), number and characteristics of patients/healthy volunteers included in the different studies and brief description of used validated assays should be given. PK data is usually obtained from healthy volunteers, as well as patients.

Comment on what is required for this specific product (e.g. NCE: full PK documentation), and on quality of clinical overview (expert report) and GCP status of PK studies.

Specifically address if pharmacokinetic data in the paediatric population is available (c.f. special populations).

Each section or subsection of the assessment report should contain 2 paragraphs:

The factual study results [Data from CTD modules 5.3.1, 5.3.2, 5.3.3 and PK/PD from 5.3.4 under relevant sub-headings], preferably in tables [with a reference to the clinical summary (module 2.7), individual reports or assessor's table].

Include assessor's comments where necessary.

The different studied pharmacokinetic parameters could be inserted into a single general summary table(s), in the introduction. When commenting on the different pharmacokinetic parameters, cross-reference may be made to this table(s).

Depending on the type of application, subheadings under 'Pharmacokinetics' may be deleted or changed, as appropriate.

For similar biological medicinal products the relevant guidelines (EMEA/CHMP/42832/2005 Guideline on similar biological medicinal products containing biotechnology derived medicinal products as active substances: non-clinical and clinical issues) and annexes have to been taken into consideration.

The clinical comparability exercise is a stepwise procedure that should begin with pharmacokinetic (PK) and pharmacodynamic (PD) comparative studies followed by comparative clinical efficacy trial(s) versus the chosen reference medicinal product authorised in the EU. In certain cases, pharmacokinetic/pharmacodynamic (PK / PD) studies for

demonstrating therapeutic equivalence is sufficient.

2.1.2. Methods

- **Analytical methods**

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

Assessor's comment

- **Pharmacokinetic data analysis**

Brief description of pharmacokinetic methods and statistical methodology (e.g. non-compartmental analysis, Population PK analysis, Physiologically based pharmacokinetic (PBPK) modelling, regression models).

Assessor's comment

- **Evaluation and Qualification of Models**

The evaluation and/or qualification of a model depend on the intended purpose and the regulatory impact which is directly linked to the risk to the patient in case the modelling predictions or assumptions lead to erroneous regulatory decisions. For requirements on POP-PK and PBPK reference can be made to the relevant guidelines. Discuss the validity of the model for use for the intended purpose, including modelling assumptions. Discuss uncertainties in model input and output.

Assessor's comment

- **Statistical methods**

Assessor's comment

2.1.3. Absorption

Data from CTD module 5.3.1 to 5.3.3 - if appropriate, studies are inserted here and tabulated whenever possible (e.g. rate and extent of absorption, involvement of active transport proteins in absorption).

- **Bioavailability**

Data from CTD module 5.3.1.1 - reports on Biopharmaceutical studies are inserted here. Absolute and relative bioavailability.

Assessor's comment

- **Bioequivalence**

Data from bioequivalence studies between formulations used in clinical studies and final formulation to be marketed.

Reference should be made to bioequivalence studies carried out to address equivalence for manufacturing changes during the development and to justify changes between clinical trials formulation and finished product intended for marketing.

For biological or biotechnology products this part should be expanded to cross-refer also to pre-clinical and functional assays.

Comparative PK studies designed to demonstrate equivalence between the similar biological medicinal product and the reference product with regard to key PK parameters are an essential part of the comparability exercise. Specific considerations related to the inherent characteristics of proteins are described in the Guideline on clinical investigation of the pharmacokinetics of therapeutic proteins (EMEACHMP/89249/2004/.

The reference product (used in clinical trials) should be indicated and it should be clear if the reference product is authorised in the EU.

Assessor's comment

- **Influence of food**

Data from food-interaction studies

Assessor's comment

2.1.4. Distribution

Volume of distribution, protein binding in-vitro and ex-vivo, distribution to tissues and red blood cells.

Assessor's comment

2.1.5. Elimination

Elimination route (metabolism, excretion unchanged renally and biliary), clearance, half-life.

- **Excretion**

Routes of excretion of the product. Fraction of the amount of product that is excreted unchanged. Involvement of active transport proteins for products that are renally secreted.

Assessor's comment

- **Metabolism**

Identification of metabolites, extent of metabolism, metabolic routes, enzymes involved in metabolism. Contribution of metabolites to effect. Data from in-vitro and in-vivo studies.

Assessor's comment

- **Inter-conversion**

Relevant for chiral products

Assessor's comment

- **Pharmacokinetics of metabolites**

Pharmacokinetic information available for active metabolites, and if available also inactive metabolites.

Assessor's comment

- **Consequences of possible genetic polymorphism**

Evaluation of consequences if polymorphically expressed enzymes (e.g. CYP2D6, CYP2C19, N-acetyl transference) are involved in the metabolism.

Assessor's comment

2.1.6. Dose proportionality and time dependency

- **Dose proportionality**

Dose proportionality after single dose and at steady state.

Assessor's comment

- **Time dependency**

Systemic exposure after (single and) multiple dose administration of the therapeutic dose and evaluation of time dependency.

Assessor's comment

2.1.7. Intra- and inter-individual variability

Data on intra- and inter-individual variability in pharmacokinetic parameters, preferably in the target population. If population pharmacokinetic analyses are available, data on intra- and inter-individual variability can be taken from these analyses.

Assessor's comment

2.1.8. Pharmacokinetics in target population

Available PK of parent compound and active metabolites in target population with special emphasis on differences from healthy volunteers including variability in patients. PK population, if available.

Depending on amount of information different sub-headings can be included.

If pharmacokinetics has mainly been documented in the target population and not in healthy volunteers, this section is removed and in the pharmacokinetics in target population is given above.

Assessor's comment

2.1.9. Special populations

Available PK of parent drug and active metabolites in special populations.

Data from CTD module 5.3.3.3 Intrinsic factor PK study reports and CTD module 5.3.3.5 Population PK study reports (the presentation of data should be similar as in preceding sections and could be included in the single general summary table).

Exploratory analysis of data across studies that may contribute to the understanding of variations in drug pharmacokinetics and possible statements on the consequences may be displayed here. These variations may be related to extrinsic or intrinsic factors such as age, gender, race, smoking status, metabolic polymorphism, renal function and hepatic insufficiency. Results of Population PK covariate analyses should be presented.

- **Impaired renal function**

Assessor's comment

- **Impaired hepatic function**

Assessor's comment

- **Gender**

Assessor's comment

- **Race**

Assessor's comment

- **Weight**

Assessor's comment

- **Elderly**

	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			

This table will be relevant for the majority of medicinal products. Specific

PK studies 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.

Assessor's comment

- **Children**

Assessor's comment

Assessor's overall comments on pharmacokinetics in special populations

Has the pharmacokinetics of parent drug and active metabolites been sufficiently documented in special populations?

Has adequate information regarding pharmacokinetics in special populations and possible lack of information been included in the SPC (restrictions/precautions/dose adjustments)?

Have Population PK analyses been conducted and have all important covariates been explored to explain interindividual or intra-individual variability in PK? Do exposure-response or PK/PD analyses together with clinical data suggest that unexplained or explained variability in PK may change the benefit-risk profile of the medicine in certain clinical scenarios and thus specific risk minimisation measures should be included in the RMP such as restrictions/precautions/dose adjustments in special populations or therapeutic drug monitoring or a post-authorisation safety or efficacy study.

2.1.10. Interactions

Critical presentation of study results.

Comments on drug-drug interactions should be provided if data are available (the presentation of data should be similar to preceding sections and should preferably be included in a summary table).

- **In vitro**

Data from CTD module 5.3.2 in-vitro studies using human biomaterials.

Assessor's comment

- **In Silico**

Populate with data from various eCTD modules depending on the question being answered.

Discuss the role of PBPK models. How do simulated data compare to the in vivo data. Discuss confidence in in–silico predictions based on submitted or literature data and the impact on dosing recommendations. Is the in house or commercial PBPK platform qualified for the intended purpose?

Assessor's comment

- **In vivo**

Data from CTD module 5.3.3.4 Extrinsic factor PK study reports.

Assessor's comment

Assessor's overall comments on interactions

Comments regarding performed interaction studies.

Have appropriate conclusions been drawn from the performed in vivo studies?

Do PBPK modelling or POP PK modelling support in vivo data? Do PBPK and POP PK suggest additional PK interactions?

Are there any other potential clinically relevant interactions e.g. inhibition or induction of enzymes/transporters that have not been studied? Are additional in vitro, in vivo or in silico drug interaction studies needed and can these be done post-authorisation?

Do exposure-response or PK/PD analyses together with clinical data demonstrate that PK interactions may change the benefit-risk profile of the medicine in certain clinical scenarios and thus specific risk minimisation measures should be included in the RMP such as restrictions/precautions/dose adjustments or therapeutic drug monitoring.

For further guidance, please consult the Guideline on the investigation of Drug Interactions http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129606.pdf

2.1.11. Exposure relevant for safety evaluation

Summarise the exposure expected in the target population at steady state, and also in specific sub-populations with increased exposure. To be used in preclinical safety evaluation of exposure margins.

Assessor's comment

2.1.12. Assessor's overall conclusions on pharmacokinetics

The content of this paragraph could be carried forward to the "overview module" of the assessment.

A self-standing and focused elaboration might therefore be necessary to allow the reader comprehensive access to the relevant findings thus enabling adequate benefit risk assessment.

In this section the assessor should 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.).

As an alternative this section could simply state the main conclusions in which case the text in the "overview module" should be elaborated on separately.

Highlight any areas of agreement/disagreement with the "clinical overview" in the submitted dossier.

2.2. Pharmacodynamics and Pharmacokinetics-Pharmacodynamycs (PK/PD)

2.2.1. Introduction

Short background on the studies performed; characteristics of healthy volunteers/patients, study design and endpoints.

For similar biological medicinal products the pharmacodynamic effect of the test and the reference products should be compared in a population where the possible differences can best be observed. The design and duration of the studies must be justified. Combined PK / PD studies may provide useful information on the relationship between exposure and effect. The selected dose should be in the steep part of the dose-response curve. Studies at more than one dose level may be useful.

If PK/PD studies are used to demonstrate similarity of the biological medicinal products, care should be taken to investigate a reasonable dose range to demonstrate assay sensitivity (see ICH E10 topic). The margins defining equivalence of PK and PD parameters must be defined a priori and justified.

2.2.2. Mechanism of action

The mode of pharmacodynamic action in relation to the clinically desired primary physiological (therapeutic) effects (primary

pharmacodynamic action) could be described. The relevance of chosen PD biomarkers could also be discussed here or below.

In addition, taking into consideration the nature of the substance under investigation potential secondary pharmacodynamic actions should be discussed.

If available briefly discuss mechanistic modelling preclinical work to characterise the mechanism of action (MoA). Please refer to the non-clinical assessment report for more detailed information.

Do the clinical PK/PD models provide further insight on the proposed mechanism of action? Consistency shown in clinic with the preclinically identified MoA and mechanistic modelling is a compelling demonstration of Proof of Mechanism.

Assessor's comment

2.2.3. Primary pharmacology

The design of the studies including PD endpoints should be critically commented on in terms of clinical relevance of biomarkers, range of doses tested and number of individuals/time of PK and PD samples included. These studies are conducted at early stage of clinical development to elucidate the mechanism of action, provide preliminary proof of concept (PoC) and to characterise the range of exposures or doses that are likely or not to have a therapeutic effect in patients and to be further investigated in dose ranging efficacy and safety trials.

In addition these studies should investigate covariate effects on primary pharmacology i.e. effects of age or genetic polymorphism on PK/PD relationships. It is acknowledged that often the extent of population exposure in early phase of development may be limited and further covariate analyses should be conducted in later stages of development, even post marketing.

Any modelling and simulation approaches used to link dose, exposure and PD, including covariate effects should be assessed. In particular consistency of assumptions on primary pharmacology across preclinical development and throughout clinical development, as tested in iterative loops of learning and confirming should be assessed.

Results from special studies (e.g. immunogenicity and microbiology) could be described here.

Early dose finding studies are particularly important to describe.

This is aimed at describing the selection of doses for the confirmatory dose-response studies based on parameters of efficacy and tolerability

in escalating dosing. The objective is the early understanding of the therapeutic width and to define the dose response of the product.

Describe any genetic difference in PD response as well as potential differences in the paediatric population (e.g. due to maturation).

Results from special studies (e.g. immunogenicity and microbiology) could be described here.

Assessor's comment

2.2.4. Secondary pharmacology

Consider the secondary pharmacology (as related to the indications). General features of tolerability in healthy volunteers with regard to secondary pharmacology on relevant dynamic endpoint studies, e.g. 24-hour blood pressure, biochemistry, virus levels, ECG, EEG etc.

As discussed in the primary pharmacology, describe modelling and simulation approaches to link dose, PK, biomarkers to clinical efficacy and safety, identify covariate effects and discuss how this information can inform the benefit-risk profile for reflecting in the SmPC and RMP.

Assessor's comment

2.2.5. Pharmacodynamic interactions with other medicinal products or substances

Assessor's comment

2.2.6. Genetic differences in PD response

Assessor's comment

2.2.7. Relationship between plasma concentration and effect

Data from CTD module 5.3.4 on PK/PD in healthy volunteers and patients.

If available, exposure-response and PK/PD approaches based on data across studies should be described here. Were these analyses used to define the time course of drug effects, the range of doses tested in early clinical development? Was the selection of dose(s) and study duration for phase III supported by these analyses? Is exposure-response adequately characterised? In addition the covariate effects on PK/PD and exposure-response relationships can be presented to identify clinical scenarios when the benefit-risk profile of the medicine may be altered resulting in the need for specific risk minimisation measures.

Results of the analyses may be also displayed in the following sections depending on the anticipated regulatory impact:

Under Clinical Efficacy; if the analyses are used to support efficacy conclusions or to identify subgroups with higher or lower response to treatment and in need for separate B:R discussions, dose adjustments or RMP follow up.

Under Clinical Safety; If the analyses are used to identify subgroups with higher or lower safety risks and in need for separate B:R discussions, dose adjustments or RMP follow up.

Assessor's comment

2.2.8. Assessor's overall conclusion on pharmacodynamics and PK/PD

The content of this paragraph could be carried forward to the "overview module" of the assessment.

A self-standing and focused elaboration might therefore be necessary to allow the reader comprehensive access to the relevant findings thus enabling adequate benefit risk assessment.

In this section the assessor should highlight the critical issues that have been identified in the different sections of the report and conclude on the quality of the pharmacodynamic documentation with special emphasis on identified deficiencies.

As an alternative, this section could simply state the main conclusions, in which case the text in the "overview module" should be elaborated on separately.

Highlight any the areas of agreement/disagreement with the "clinical overview" in the submitted dossier and comment on the suitability of the SPC.

3. Clinical efficacy

General Guidance

The report should be sufficiently detailed to allow for secondary assessment by other CHMP experts.

Although this report should include the necessary details to understand what is in the file you are requested to focus on the salient findings and those deficiencies that justify the questions intended for the

applicant with a discussion/interpretation of the results giving the grounds for the benefit-risk assessment and the CHMP recommendations!

Indiscriminate copying from the applicant's dossier ("Overview" and "Summary" into the AR is not acceptable!

Hence, decide on the minimum detail on individual studies (aim: balanced presentation of "positive" and "negative" findings).

Distinguish (also in comments) between pivotal trials and supportive trials based on judgement on individual importance (mention all studies, if possible, referring to tabulated summaries).

The use of tables/graphs/figures is encouraged (rather than lengthy text!)

There should be a clear separation between data submitted and assessor's comments on that data.

Critical assessment (e.g. comments on the validity and interpretation of the data, conclusions) should be described in the "Assessor's comments" sub-sections that follow each chapter. The words 'Major objection' – see proposed List of Questions, may be used when necessary to cross-refer to the LoQ.

The report should indicate whether additional expertise is needed e.g. a SAG meeting to address some unresolved clinical issues or the need for further assessment of pharmacovigilance issues.

The report should emphasise findings that need to be reflected in the SPC.

3.1. Introduction

Use a brief introductory statement on the general features of the submitted data and the sought indication.

A tabular overview of the relevant clinical studies; study number, design and number of patients in treatment arms, baseline characteristics such as age, gender and severity of disease, efficacy parameters and efficacy results should be included. Such a table should be in accordance with the CTD table 2.7.3.1, as appropriate.

If relevant for the therapeutic indication, describe the experience in special populations to complement what is mentioned under section III.3.

If applicable, include details about Scientific Advice on Clinical Efficacy (detailed paragraph on advice sought and given).

Include conclusive statement on compliance with GCP, (to be carried forward to I.2 GCP aspects and the "overview module").

Example table for study details:

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered/ compl.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoint

Assessor's comment

3.2. Dose-response study(ies)

Objectives:

- *Dose selection*
- *Characterise Dose Exposure Response (D-E-R)*
- *Provide Proof Of Concept (PoC)*

Design - Methods:

Please briefly describe study designs and methods of studies contributing to selection of one or more doses in the main (pivotal) studies. Please consider size, number and range of studied doses and justification of surrogate endpoints.

Consideration should be paid to the study objectives, the validity of the approach for the specifics of the design, and vice versa e.g. If a regression model is being fitted to characterise the D-E-R relationship, sufficient number and range of doses will need to have been studied.

Depending on the endpoints used in the studies (PD vs. Clinical endpoints) you may cross refer to the clinical pharmacology section.

As PK/PD modelling and simulation methods are considered important to support dose selection as well as D-E-R characterisation and PoC, please include the most relevant methods and refer to relevant sections for detail.

Please discuss results and outline how these contributed to the objectives of dose and dosing schedule selection, characterisation of D-E-R relationship and PoC.

Assessor's comment

3.3. Main study(ies)

The methods and results should be presented and discussed as relevant for each of the studies, which should be identifiable in the text (e.g. per protocol number). Tables are encouraged.

A detailed checklist on the description of trial methods, results and discussion is reported below ("The CONSORT statement"- The Lancet 2001; 357: 1191-94, modified). This extensive checklist is not a requirement; rather, it provides an ordered list of potential items to be included. The relevance of each item and, if appropriate, the required level of detail, needs to be considered on a case-by-case basis.

Critical comments should be included, as appropriate.

Identification and description of the study.

Include the number and title of the study. This should already indicate how participants were allocated to treatment arms (e.g."random allocation", "randomised", or "randomly assigned").

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

Assessor's comment

Methods

Keep to most relevant items (see bullets hereafter), on a case-by-case basis.

- **Study Participants**

Inclusion/exclusion criteria, locations (e.g., regions where the recruiting sites were located) and settings (type of recruiting sites,e.g. type of hospital/ward) where the data were collected.

Assessor's comment

- **Treatments**

Precise details of treatment (or other type of interventions) intended for each group and how/when they were intended to be administered.

Assessor's comment

- **Objectives**

Specific objectives and hypotheses. State the statistical hypothesis (e.g. superiority, equivalence or non-inferiority for the primary

endpoint(s)) and any justification provided for the plausibility of the expected effect size or choice of delta.

Assessor's comment

- **Outcomes / endpoints**

Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (e.g., multiple observations, training of assessors, central/independent reviews).
If appropriate, focus on the most important secondary endpoints.
Describe justifications provided by the applicant to support the validity of any surrogate end-points, if applicable.

- *Discuss the validity of any surrogate endpoints.*
- *Brief comments on the clinical relevance of the aforementioned endpoint(s).*

Assessor's comment

- **Sample size**

How sample size was determined and, where applicable, explanation of any interim analyses and stopping rules.

Assessor's comment

- **Randomisation**

Methods used to generate the random allocation sequence and stratification criteria to implement it.

Assessor's comment

- **Blinding (masking)**

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.

Assessor's comment

- **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); methods for additional analyses, such as subgroup analyses and adjusted analyses.

- *Acceptability of the statistical analysis plan.*
- *Discuss any deviations from the pre-specified statistical analysis plan.*

Results

Keep to most relevant items (see bullets hereafter), on a case-by-case basis.

- **Participant flow**

Study Participant flow.

Describe the flow of the progress of study participants through all the phases of the trial (use of a diagram, as suggested below (or alternatively a table) should be used whenever possible).
Specifically, for each group, report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analysed for the primary outcome, e.g.:

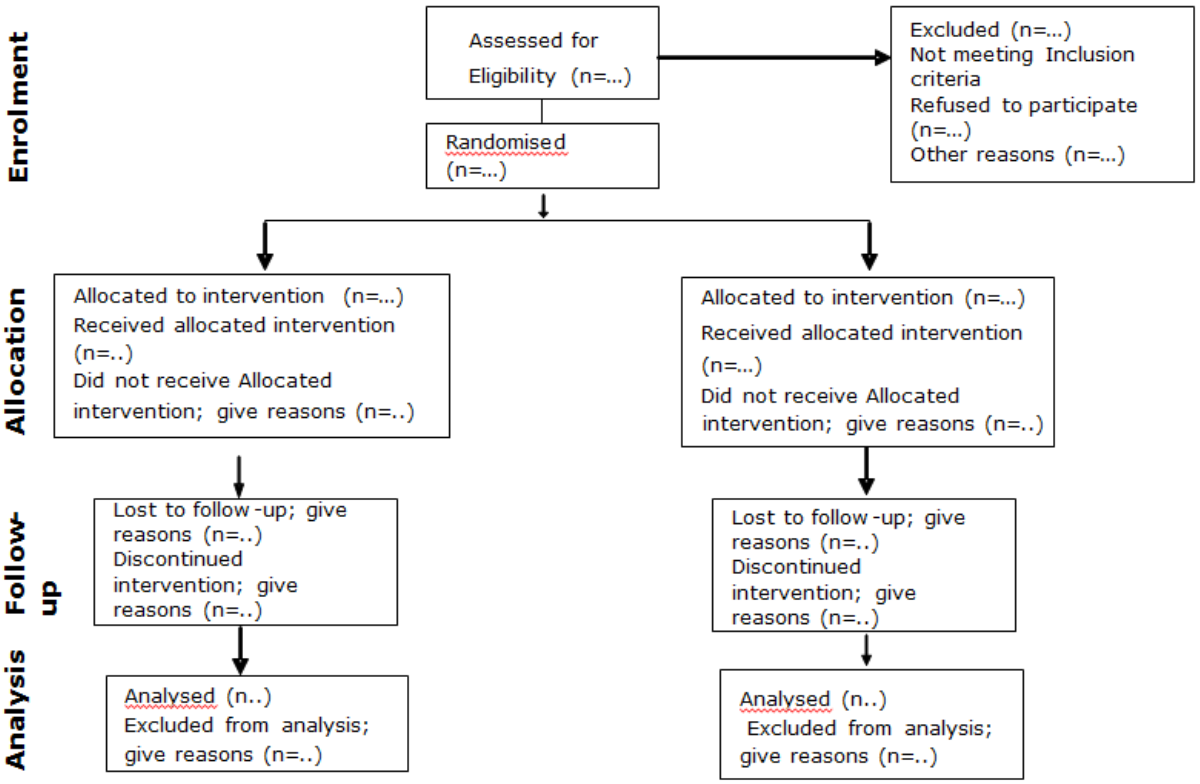
1. Enrolment (No. subjects screened; No. randomised; No. excluded and reason, dates defining the periods of recruitment).

2. Allocation (by treatment arm, No. randomised, No. started allocated treatment, No. that did not start allocated treatment and reasons).

3. Follow-up (by treatment arm, No. lost to follow-up and reasons; No. protocol treatment discontinuation; dates defining the periods of follow-up).

4. Analysis (No. included into set for analysis of primary endpoint; No. excluded and reasons).
Describe protocol deviations from study as planned, together with reasons.
Describe criteria for treatment rescue and for early escape if relevant for the understanding of the interpretation of the results.

Use and amend as appropriate)



Assessor's comment

- **Recruitment**

Dates defining the periods of recruitment and follow-up.

Assessor's comment

- **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.

Assessor's comment

- **Baseline data**

Baseline demographic and clinical characteristics of each group.

Describe particularly any asymmetry in characteristics across treatment arms.

- *Discuss how study population reflects intended indication (or defer to overall conclusions).*

- *Discuss similarities and any discrepancies between treatment arms (if applicable).*
- *Discuss treatment compliance, if appropriate.*

Assessor's comment

- **Numbers analysed**

Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention to treat". State results in absolute numbers when feasible (e.g., 10/20 not 50%).

Assessor's comment

- **Outcomes and estimation**

For each primary and secondary outcome, provide a summary of results for each group with estimated precision (e.g. 95% CI).
Clinical relevance of the observed effect should be described since it may be particularly important for the benefit /risk assessment.

Assessor's comment

- **Ancillary analyses**

Address multiplicity by reporting any other analysis performed, including subgroup analyses and adjusted analyses, including pre-specified and exploratory ones (subgroup analysis and other post hoc techniques).
Modelling and Simulation (M&S) analyses (e.g. POP-PK, POP-PK PD) to further characterise D-E-R and impact of intrinsic/extrinsic factors in a more diverse population may be included as ancillary analyses.
Discuss consistency of results with prior knowledge of D-E-R and clinical outcomes. Refer to section 2.2 Pharmacodynamics and PK/PD.
Justifications for choice of analysis should be assessed.

Assessor's comment

- **Summary of main efficacy results**

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

The following template table should be used to display the data for the specific studies. The level of detail should be adjusted to the data later needed for the discussion and conclusion on benefits, as well as the benefit-risk assessment. Treatment groups should be presented in separate cells, and so should be information on different analysis sets (e.g. ITT and PP). Reasons for drop-outs should be summarised. Different main trials should be presented in separate tables. No additional text is foreseen in this section apart from these tables. A detailed description of these trials with for instance information on design and power calculation is presented in other sections. The safety data is subject to the section "Clinical safety".

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

Table XXX. Summary of efficacy for trial <trial>

<table>
<tr><td colspan="4"><u>Title:</u> <title> {as indicated on the study report}</td></tr>
<tr><td>Study identifier</td><td colspan="3"><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}</td></tr>
<tr><td rowspan="4">Design</td><td colspan="3"><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.}</td></tr>
<tr><td colspan="2">Duration of main phase:</td><td><time></td></tr>
<tr><td colspan="2">Duration of Run-in phase:</td><td><time> <not applicable></td></tr>
<tr><td colspan="2">Duration of Extension phase:</td><td><time> <not applicable></td></tr>
<tr><td>Hypothesis</td><td colspan="3"><Superiority> < Equivalence> <Non-inferiority> <Exploratory: specify></td></tr>
<tr><td rowspan="3">Treatments groups
{add as many rows as needed to describe the treatment groups}</td><td colspan="2"><group descriptor>
{provide abbreviation for use later in the table of the results section}</td><td><treatment>. <duration>, <number randomized></td></tr>
<tr><td colspan="2"><group descriptor></td><td><treatment>. <duration>, <number randomized></td></tr>
<tr><td colspan="2"><group descriptor></td><td><treatment>. <duration>, <number randomized></td></tr>
<tr><td rowspan="2">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}</td><td><Co->Primary endpoint</td><td><label>
{generate abbreviation for use later in the table of the results section}</td><td><free text> {provide brief description}</td></tr>
<tr><td><Secondary> <other: specify> endpoint</td><td><label></td><td><free text> {provide brief description}</td></tr>
</table>

	<Secondary> <other: specify> endpoint	<label>	<free text> *{provide brief description}*
Database lock	<date>		

Results and Analysis

{present the result separate for each analysis that is considered relevant for the conclusion on the trial; in any case the pre-specified primary analysis should be presented}

Analysis description	**Primary Analysis**

Analysis population and time point description	<Intent to treat> <Per protocol> <other: specify> *{consider adding a brief description of the definition of the population}* <time point>			
Descriptive statistics and estimate variability	Treatment group	<group descriptor> *{as per above terminology}*	<group descriptor> *{as per above terminology}*	<group descriptor> *{as per above terminology}*
	Number of subject	<n>	<n>	<n>
	<endpoint> *{label as above}* (<statistic>) *{e.g. mean, median, etc}*	<point estimate>	<point estimate>	<point estimate>
	<variability statistic> *{e.g. standard deviation, confidence interval, etc}*	<variability>	<variability>	<variability>
	<endpoint> (<statistic>)	<point estimate>	<point estimate>	<point estimate>
	<variability statistic>	<variability>	<variability>	<variability>
	<endpoint> (<statistic>) <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	Comparison groups	<group descriptors>
		<test statistic>	<point estimate>
		<variability statistic>	<variability>

	{indicate endpoint using terminology as per section "Endpoint and definitions}	P-value	<P-value>
	<<Co->Primary ><Secondary><other: specify> endpoint	Comparison groups	<group descriptors>
		<test statistic>	<point estimate>
		<variability statistic>	<variability>
		P-value	<P-value>
Notes	<free text> *{consider amongst others the following information:* *- reasons for drop-outs* *- critical findings with regard to the analysis}*		
Analysis description	**<Secondary analysis> <Co-primary Analysis> <Other, specify: >** *{also indicate if the conduct of the analysis was pre-specified}*		

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

3.4. Clinical studies in special populations

Special studies e.g. in children, in the elderly and in patients with renal or hepatic impairment. Describe these studies as suggested for the main studies including considerations on dose adjustments.

	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			

This table is relevant for the majority of medications. 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 RCTs in older subjects should be presented or the absence of such studies should be acknowledged.
Statements made after consideration of these data should be meaningfully reflected in the product information.

Assessor's comment

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

Criteria used for these analyses should be stated and may involve exploratory analysis on the whole database considering different effect modifiers (gender, age, drug-disease interactions, smoking etc.).
In addition dose-effect relationship in special population may need consideration (weight, creatinine clearance etc.).
Refer also to Section 2.2.7 Relationship between plasma concentration and effect.

Assessor's comment

3.6. Supportive study(ies)

These should be concisely addressed adopting a cumulative approach. For biopharmaceuticals, antibody formation should be mentioned with regard to efficacy (e.g. neutralising antibodies).

Assessor's comment

3.7. Assessor's overall conclusions on clinical efficacy

Discussion on clinical efficacy

The discussion is often the most important part of the assessment report. In terms of structure it should in principle follow the flow of the presentation of results above.
Try to be as clear and concise as possible (often discussions are too long and verbose, and the true meaning of the data is not addressed).

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

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

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

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

4) Highlight important issue that are expected for CHMP discussion

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

Design and conduct of clinical studies

- *Was the design of the studies adequate (randomised active and placebo controlled trials)? If not, what are the justifications and are they acceptable?*
- *Was the patient population adequately selected (reflection on inclusion/exclusion criteria)?*
- *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 consideringregulatory guidance/scientific advice. Validity of surrogate markers to replace hard endpoints? Acceptability of a composite endpoint and its domains?*
- *Adequacy of the methods, conduct, analysis and reporting of results from main studies, as appropriate. Discuss any particular issues raised regarding the study design.*
- *Is the design in accordance with legal requirements, available guidelines, scientific advice?*
- *What are the implications of any GCP inspection?*

Efficacy data and additional analyses

- *Magnitude and clinical relevance of the effect. Clinical relevance of the observed effect should be described since it may be particularly important for the benefit /risk assessment.*
- *What are the key findings (or uncertainties)? What key findings (or uncertainties) should be part of the benefit-risk assessment?*
- *Generalisability (external validity) of trial findings. Do the results support the claimed indication?*

- *Is the D-E-R (efficacy) relationship well characterised and the intrinsic extrinsic factors affecting this relationship well understood?*
- *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)*
- *Discuss any justifications for waiving certain studies or replacing original studies by literature data*

- *Lack of information in certain groups of patients (children, elderly women with childbearing potential etc.) should be mentioned to qualify statement made in section 4.4 of the SPC and it should be mentioned here and summarised in the overall conclusion if follow-up studies have been requested by the CHMP.*
- *Which are specific considerations for the paediatric population?*
- *For similar biological medicinal products mention explicitly the comparative nature of the results obtained with the chosen reference medicinal product.*
- *How are the findings (or lack of information) reflected in the SPC? Ensure correspondence with SPC (particularly section 5.1) and that all information in the SPC is explicitly assessed and supported by the scientific assessment.*
- *Mention if there are any outstanding data, which remain as post-authorisation measures/SO and if this is reflected in the SPC.*

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.

Conclusions on clinical efficacy

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

4. Clinical safety

The safety data should consider the experience available from all patients exposed and therefore should be presented as an integrated analysis. However study-specific features related to clinical safety should be described and the interpretation provided.

Recall concerns identified in non-clinical studies with potential for human use (e.g. toxicity, human metabolites not produced in animals) and in pharmacodynamic studies.
Whenever there is an impact on the Benefit / Risk, please elaborate here on the clinical issue (s) that led to this conclusion:
[Note regarding Obligation to complete post-authorisation measures: In a limited number of cases, data that are considered as "key" to the benefit risk balance may be requested as a condition of the MA. In case issues have been identified for inclusion in Annex II as conditions, use the following statement. Any measure identified as a condition needs to be well motivated, notably the need for a condition should be explained in the context of a positive benefit/risk balance.

In particular, conditions related to post-authorisation efficacy studies should explicitly refer to situation(s) as listed in the Commission Delegated Regulation (EC) No 357/2014.]

4.1. Introduction

Brief introductory statement on the general features of the submitted data.
For similar biological medicinal products, the clinical safety assessment should highlight any potentially significant clinical differences in terms of the safety profile between the reference and the similar medicinal product.
Special emphasis has to be put on the immunogenicity aspects such as the incidence and characteristics of antibodies. In addition, any consequence for specific post marketing surveillance or pharmacovigilance monitoring should be considered (see further CHMP/3097/02 Note for Guidance on Comparability of Medicinal Products containing Biotechnology-derived Proteins as Drug Substance - Non Clinical and Clinical Issues).

Assessor's comment

4.2. Patient exposure

List clinical studies contributing to safety (summary tables are encouraged)(Cut-off date should be stated).
Number and characteristics of included patients (age, stage/severity of disease) and healthy subjects, (could be included in the summary table). Size of the database at 6 months and 12 months if appropriate for long-term treatment.
Particularly indicate the safety database for paediatric patients by age groups where appropriate, if applicable.

Example of a table: Patient exposure (cut off)

	Patients enrolled	Patients exposed	Patients exposed to the proposed dose range	Patients with long term* safety data
Placebo-controlled				
Active -controlled				
Open studies				
Post marketing				
Compassionate use				

* In general this refers to 6 months and 12 months continuous exposure data, or intermittent exposure.

In general this refers to 6 months and 12 months continuous exposure data, or intermittent exposure.

Any information on exposure >12 months should be provided
Discuss any limitations of the safety database in relation to the proposed target population

Assessor's comment

4.3. Adverse events

Results should be given by the System Organ Classification (SOC), preferred term including data on severity of all adverse events. A summary table as in CTD (2.7.4.3) is necessary with statistical analyses.

In all cases, the relationship between adverse events and reactions (causality included) and other variables should be addressed.

For example, variables may be:

- *Duration of treatment.*
- *Dose regimen and schedule.*
- *Cumulative and dose related toxicity.*
- *Co-morbidity and co-medication as appropriate.*

The investigation of D-E-R (safety) relationships can reinforce the assessment of safety in special populations, the clinical impact of drug-drug interaction (DDI) and identify clinical scenarios where D-E-R may be altered. Any uncertainties in D-E-R (safety) with clinical consequences may be reflected in the RMP.
Reversibility of the event should be addressed as appropriate.

Comment on confirmation of non-clinical findings as appropriate. Possible relationship with manufacturing/quality issues should be mentioned if relevant (e.g. antigenic compounds).

In case of similar biological medicinal products, even if the efficacy is shown to be comparable, the similar biological medicinal product may exhibit a different safety profile (in terms of nature, seriousness, or incidence of adverse reactions). Pre-licensing safety data should be obtained in a number of patients and for exposure duration sufficient to address the comparability of the adverse effect profiles of the test and the reference product. Care should be given to compare the type, severity and frequency of the common adverse reactions between the similar biological and the reference biological medicinal products.

Assessor's comment

4.4. Serious adverse events and deaths

Following the overall safety profile, a separate analysis of the serious adverse events and deaths should be made.
Results should be given by the SOC (preferred term) including data on severity of serious adverse events. Summary table as in CTD (2.7.4.3 and 2.7.4.6) is necessary.
In all cases, the relationship between serious adverse events/death, and other variables should be addressed:

For example, variables may be:

- *Duration of treatment.*

- *Dose regimen and schedule.*
- *Cumulative and dose related toxicity.*
- *Co-morbidity and co-medication as appropriate.*
- *Reversibility / outcome (excluding death) of the event.*

Assessor's comment

4.5. Laboratory findings

Safety laboratory markers may be more sensitive to pick up clinical safety issues (arguably not always specific) or sometimes even predictive of AE. If available, PK/PD M&S or regression D-E-R (R= Lab biomarkers) analyses, may give further insights in the D-E-R (safety) relationship and the intrinsic and extrinsic covariates of importance.

Assessor's comment

4.6. Safety in special populations

Short summary of all available information both derived from preclinical and clinical studies in order to substantiate the specific statements in the SPC (e.g. gender related differences, risks for the use in pregnant women, effect anticipated or observed in children (in the relevant age groups), elderly, etc). D-E-R (safety) analyses and graphs may be very informative in this respect (see above).
In general, the wording should be concise and details beyond basic information should only be given when relevant for the critical assessment.

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.

Assessor's comment

4.7. Immunological events

Antibody formation should be mentioned with regard to safety (e.g. neutralising antibodies, auto-antibodies, species-specific antibodies, such as HAMA (human anti-mouse antibodies), HAHA (human anti-human antibodies) in the case of monoclonal antibody products. Discuss the validity/usefulness of the assay. PK/PD M&S may be helpful in understanding the PK profile of antibodies and impact on safety or efficacy.

Assessor's comment

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

Pharmacokinetic and pharmacodynamic interaction-information directly relevant for safety should be mentioned here. Clinical relevant safety experience obtained from other concomitant use should also be considered.

Assessor's comment

4.9. Discontinuation due to AES

Brief detailing, maybe cross- reference to CTD table (2.7.4.5).

Assessor's comment

4.10. Post marketing experience

Identify new information obtained from post-marketing experience.

Assessor's comment

4.11. Assessor's overall conclusions on clinical safety

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.
- Is the D-E-R (safety) relationship well characterised and the intrinsic extrinsic factors affecting this relationship well understood?

- 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?
- Are there expected and/or anticipated (predicted) safety concerns from the clinical pharmacology programme to be included in the RMP?

- 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 post-authorisation measures and if this is reflected in the SPC. Additional post-marketing studies/FUM?

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

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).

5. Risk management plan

The CHMP rapporteur should assess the safety specification within the RMP, and complete the sections below. The CHMP Co-Rapporteur should not assess the safety specification within the RMP, but should flag safety findings which may be relevant for the RMP.

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

In case of a line extension, the assessment focusses on the changes made to the RMP.

5.1. <Safety Specification>

The rapporteur considers the data presented in the RMP as follows:

Guidance: There is no need to copy and paste the information from the RMP under the below bullet points. Those sections can be left blank unless there are aspects in those sections that require amendments and could lead to questions in the D120 LOQ.

- **Epidemiology of the indications and target population**

[This corresponds to Module SI of the Safety Specification of the RMP]

- **Clinical trial exposure**

[This corresponds to Module SIII of the Safety Specification of the RMP. The information should have been already addressed in section 4.2 Patient Exposure of this AR.]

- **Populations not studied in clinical trials**

[This corresponds to Module SIV of the Safety Specification. These aspects should have been already considered in section 4.2].

- **<Post-authorisation experience>**

[This corresponds to Module SV of the Safety Specification. These aspects should have been already considered in section 4.10.]

Assessor's comment

[Comments on the four afore-mentioned sub-headings should be made here. Important to only comment if there are major errors/inconsistencies in the RMP from the Applicant or if the information in it is not in line with the clinical assessment. This is particularly important if comments lead to requests for an updated version of this section of the RMP and if the comments impact for example the summary of the RMP. Otherwise, simply say that the presentation in the RMP is largely acceptable.]

- **Additional EU requirements for the safety specification**

[This corresponds to Module SVI of the Safety Specification].

Potential for harm from overdose

[This is especially important for medicines used by patients with psychiatric disorders or a medicine with a narrow therapeutic margin. Serious adverse events related to overdose already discussed in section of this AR and, in general, any cases of overdose during clinical trials, should be reflected in the RMP].

Assessor's comment

[Comment on the applicant's text in the RMP on the potential for overdose. The information in this RMP section should be consistent with information to be included in section 4.9 of the SmPC. If appropriate, overdose should be included as a safety concern and appropriate risk minimisation proposed in RMP part V.]

<Potential for transmission of infectious agents>

[This is only relevant for medicines for which the safety evaluation on Adventitious Agents (Quality D80 AR: 5. Appendix, section A.2)has concluded on the possibility of a risk.]

Assessor's comment

[If any comment is deemed necessary, it should be consistent with conclusions in section 3.2.3 of the Overview AR related to Adventitious Agents.]

<Potential for misuse for illegal purposes>

[The two most important areas are whether the drug is likely to be sold on the black market or used to enable assault.}

Assessor's comment

[Comment on the likelihood based on the substance and mechanism of action, and whether this translates to a safety concern that should be addressed in the RMP.]

Potential for medication errors

[Only summarise if the Applicant's view in relation to potential for medication errors are inadequate]

Assessor's comment

[Consider the following points:

- *Is the applicant's analysis on medication errors which have occurred in the clinical trial population adequately reflected in the RMP?*
- *Availability of multiple strengths, posologies or concentrations, or where different products have different formulations, reconstitution differences etc, should be considered in the potential for medication errors.*

- *If a device is involved, has the applicant adequately analysed possible consequences of a device failure?*

Assess if medication error constitutes a safety concern and whether there have been sufficient measures put in place to minimise the risk of medication errors.]

Potential for off-label use

[Only summarise if the Applicant's view in relation to potential for medication errors are inadequate]

Assessor's comment

[Have situations where the product could intentionally be used outside the authorised indication (e.g. other disease area or target population) been adequately reflected in the RMP?

In cases where off-label use has the potential for harm beyond the safety profile of the product in the target population, this should be considered for inclusion as an important potential risk.]

Specific paediatric issues

[Issues identified in paediatric investigation plans.

Potential for paediatric off-label use – including non-authorised paediatric age groups. Are there particular concerns for paediatric off-label use?]

Assessor's comment

[Relevant safety aspects specific for the paediatric population are usually described in section 3.4.9 of the Overview AR. So, comment here if any of the safety issues in paediatrics should be considered as a safety concern in the RMP.

- **Identified and potential risks**

[This corresponds to Module SVII of the Safety Specification. This module of the RMP should provide information on the important identified and important potential risks associated with use of the product. These include the important identified and potential adverse events/reactions, important identified and potential interactions with other medicinal products, foods and other substances, and the important pharmacological class effects.

What constitutes an important risk will depend upon several factors including the impact on the individual patient, the seriousness of the risk and the impact on public health (see also V.B.1 in GVP). The most clinically significant risks and/or those where further characterisation of the risk is required post-authorisation should be included as important identified or important potential risks. Often these are reflected in the contraindications or warnings and precautions section of the summary of product characteristics (SmPC).

For RMPs covering multiple products where there are significant differences in the identified and potential risks for different products, it should be clear which risks relate to which product. Division of identified and potential risks using the headings below should only be considered when the risks clearly do not apply to some products and lack of separation could cause confusion. Headings which could be considered include:]

<Risks related to a specific formulation, indication or route of administration>

Examples might include an RMP with two products with completely different indications: eg sildenafil with an indication in one product for erectile dysfunction and in a second product for pulmonary arterial hypertension.

<Risks relating to a specific target population>

The paediatric population is an obvious example of a target population where there may be additional risks relating to physical, mental and sexual development which would not be relevant to a product intended solely for adult patients.

Assessor's comment

The entire description of each safety concern from the RMP should not be copied in the assessment report. For each safety concern presented by the applicant, (), briefly comment on whether a proposed safety concern is appropriate (and therefore to be forwarded to the next section on Summary of Safety Concerns) or not. If yes, comment also briefly on the adequacy of the more detailed description of the safety concern.

- **Identified and potential interactions**

[This part is reflected in the Overview AR (section 3.4.8. Safety related in drug-drug interactions). It includes Identified and potential pharmacokinetic and pharmacodynamic interactions in relation to both the treatments for the condition, but also in relation to commonly used medications in the target population. Important interactions with herbal medicines or with food should also be considered. A cross-reference to the Overview AR is normally appropriate]

Assessor's comment

[If a specific comment beyond the discussion included in section 3.4.8 of the Overview AR is made here, comments in both sections should be made consistent. If warranted, specific interactions should be considered as a safety concern.]

- **Missing information**

[This section should be built in relation to section "Populations not studied in clinical trials" and other data gaps e.g. long-term safety.]

5.2. Summary of the safety concerns

[This corresponds to Module SVIII of the Safety Specification and will be common to equivalent section in Periodic Safety Update Reports.

Table XX: Summary of the Safety Concerns as proposed by the applicant.

Summary of safety concerns	
Important identified risks	
Important potential risks	
Missing information	

Assessor's comment:

[Comment on whether the applicant's proposal for the safety specification is adequate based on the assessment of human pharmacokinetics and clinical safety data.

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

Having considered the data in the safety specification

<The rapporteur agrees that the safety concerns listed by the applicant are appropriate>

or

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

- <The rapporteur considers that> <should also be <a> safety concern(s)>
- <The rapporteur considers 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]

6. Pharmacovigilance system

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

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

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

<Provided that the deficiencies are rectified prior to the applicant placing the medicinal product on the market, the CHMP may consider that the Pharmacovigilance system will fulfil the requirements. The

applicant must ensure that the system of pharmacovigilance is in place and functioning before the product is placed on the market>

Assessor's comment

7. List of references

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

Definitions of questions:
"Major objections", preclude a recommendation for marketing authorisation. In principle, one major objection may entail more than one question and the use of bullet points or subheadings is encouraged. It is vital that the structure and content of a major objection are clear and understandable to the reader. Detailed comments may be necessary along with a reference to guidance documents.

Ideally, the objection should include a clarification as to what kind of response/action is expected from the applicant.

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

Comments should be made on the need for paediatric development in relation to questions on the clinical development
This list should be carried forward to the "overview module".

Clinical aspects

Major objections

Pharmacokinetics

Pharmacodynamics

Efficacy

Safety

Pharmacovigilance system

Other concerns

Pharmacokinetics

Pharmacodynamics

Efficacy

Safety

Pharmacovigilance system

9. Recommended conditions for marketing authorisation and product information

Points relating to this heading should also be specifically addressed in the relevant section of the "overview module", (e.g. specific comments on the product information).

User Consultation' of the package leaflet (Art 59(3) and 61(1) of the amended Directive)

The applicant has to provide results of assessments carried out in cooperation with target patient groups on the package leaflet ('user consultation') or a justification for not performing such consultation. Please refer to the relevant draft Commission and EMEA guidance documents for more information on the requirements, presentation and assessment of the 'user consultation' results: http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2005/08_05/USERTESTING_20050817.pdf

http://www.emea.eu.int/pdfs/human/euleg/27737805en.pdf

In all cases, it should be assessed and stated (see the "overview") whether 'user consultation' of the PL has been performed or is foreseen, or whether the justification for its absence is acceptable. In case a 'user consultation' of the PL has been performed and is included in the application, the (Co-)Rapporteur shall include the assessment of the results of 'user consultation' in their assessment reports, as well as a conclusion on the overall readability of the PL. A template/guidance for the assessment of user testing results is available via QRD members. Any possible deficiencies or comments/questions are to be included in the LoQ.

When 'user consultation' submitted at Day 121 and/or overall PL readability, can only be judged in the 2nd or 3rd phase of the review, the Day 150 AR or Day 180 AR should include a conclusion on the 'user consultation' assessment and overall PL readability.

(CHMP members should also review the Rapporteurs position on the requirement for 'user consultation' and his/her assessment of the 'user consultation' results or justification, and of the overall PL readability. It is up to the (Co-) Rapporteur to involve the relevant experts for the assessment of the 'user consultation' information.).

More general comments could also be made here

User Consultation