Guidance document on the content of the <co-> rapporteur day<60*><80> critical assessment report

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

Non-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

Table of contents

Non-clinical critical assessment 7

1. Introduction 7

1.1. Type of application and aspects on development 7

1.2. GLP aspects 11

2. Pharmacology (CTD MODULES 2.6.2 AND 4.2.1) 12

2.1. Primary pharmacodynamics 13

2.2. Secondary pharmacodynamics 14

2.3. Safety pharmacology 14

2.4. Pharmacodynamic drug interactions 15

2.5. Assessor's overall conclusions on pharmacology 15

3. Pharmacokinetics (CTD MODULES 2.6.4 AND 4.2.2) 16

3.1. Methods of analysis 16

3.2. Absorption 16

3.3. Distribution 17

3.4. Metabolism 18

3.5. Excretion 19

3.6. Pharmacokinetic drug interactions 19

3.7. Other pharmacokinetic studies 20

3.8. Assessor's overall conclusions on pharmacokinetics 20

4. Toxicology (CTD MODULES 2.6.6 AND 4.3.3) 20

4.1. Single dose toxicity 21

4.2. Repeat-dose toxicity 21

4.3. Genotoxicity 23

4.4. Carcinogenicity 25

4.5. Reproductive and developmental toxicity 27

4.6. Local tolerance 28

4.7. Other toxicity studies 28

4.8. Ecotoxicity/environmental risk assessment 30

4.9. Assessor's overall conclusions on toxicology 34

5. List of references 36

6. List of questions proposed by the <co->rapporteur 37

7. Recommended conditions for marketing authorisation and product information 38

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)**

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

In general the following aspects should be considered:

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

The report should describe salient findings and especially those deficiencies that justify the questions intended for the applicant. These questions will also be listed in the "overview module" of the assessment.

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.

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.

The report should indicate whether findings have implications for human safety and whether additional expertise is needed to assess this (e.g. there are findings regarding carcinogenicity but receptors are different between target species and man).

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

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 use of tables/graphs/figures is encouraged; examples are given in the template and are to be used as appropriate. PK/TK tables should include the number of animals and standard deviation for each parameter. For repeat-dose studies, TK day of sampling should be mentioned. Tables taken from the dossier may also be included into the assessment. Don't forget footnotes!

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

Please also refer to the CTD guidance text.

Non-clinical critical assessment

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), e.g. complete independent application, mixed application, well established use application, biosimilar application etc, and 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.

For each main section of the assessment report for modules 4 and 5, the report should describe the data submitted in accordance with Annex I, Directive 2001/83. The types of studies addressed within each section should include all indents as listed in Annex I. 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 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.

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.

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).

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

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

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 benefit/risk assessment and provision of adequate information to patients and prescribers.* *Discuss any deviations from conventional development plans, particularly about the timing of animal tests and the conduct of clinical trials, as described in the legislation and applicable guidelines, and any impact on the final risk-benefit assessment.*

The applicant is unable to provide comprehensive data on the efficacy and safety of the product under normal conditions of use ("exceptional circumstances" or conditional approval ")	*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 Conditional approval, the rapporteur should assess the validity of the reason(s) put forward by the applicant according to guideline on conditional Marketing Authorisation pursuant to Commission Regulation No 507/2006.. Note that conditional approval will normally not include specific obligation on the non-clinical part – exceptions are "emergency situations"*

[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.*

Aspects of development.

Introduce and comment the non-clinical development programme in view of the proposed indication and posologies (indicate if there is a paediatric indication or development). State if the range of studies is in agreement with EU/ICH guidelines (e.g. M3, S6).

Indicate if the applicant has requested accelerated assessment and the fulfilment of relevant criteria.

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 the product specific annexes related to this guideline, 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.

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 nonclinical aspects, if applicable, and state the relevant key information about the current status of the nonclinical studies (i.e. completed, studies ongoing, etc).

State if, and when Scientific Advice/Protocol Assistance has been given, describe the issues and indicate whether the advice followed by the applicant.

Indicate if, and when Orphan Drug designation has been granted. If relevant, indicate any potential similarity issues concerning mechanism of action.

In cases where batches other than the one intended for marketing was used in part of the studies, a qualification of new impurities (if any) should be assessed.

1.2. GLP aspects

Statements on GLP should be addressed here and also in the "overview module" of the assessment.

In this section specifically address:

- *Any concerns raised during the assessment about compliance with GLP requirements(data accuracy or protocol compliance).A useful tool to be used to identify the need for a triggered GLP inspection is the checklist "Triggers for audits of good laboratory practice (GLP)"*

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2015/12/WC500199238.pdf

- *Discuss the need for a GLP inspection. To request a GLP inspection:*
- *Contact your national GLP monitoring authority.*
- *Contact EMEA inspection sector - GLP inspection coordination.*
- *Determine with them the studies, sites and special concerns or issues 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).*

2. Pharmacology (CTD MODULES 2.6.2 AND 4.2.1)

- **Brief summary**

Active substance, mode of action and brief rationale for the development of the product in the proposed indication should be described.

For similar biological medicinal products this section should highlight the comparative nature of the studies and rational for the non-clinical development program. (The discussion of the results can come under point "discussion" at the end of the section.)

Assessor's comment

- **Physical chemistry**

Structure of the active substance (insert structure)

Site of labelling (see structure)
Isomerism
Molecular weight
Solubility in water
Pka
Distribution coefficient
Solubility in other solvents
Stability
Possible chirality and its consequences

Assessor's comment

2.1. Primary pharmacodynamics

This section should address PD studies in relation to the disease to be treated and the proposed indications including the following points:

- *Proof of concept (in-vitro and in-vivo) and mode of action.*
- *Availability of animal models relevant for the proposed indication/ interspecies comparison.*
- *Activity (e.g. ED50) including the species used in toxicology studies.*
- *Preliminary PK (plasma concentration) in animal models if available.*
- *Duration/reversibility of effects, resistance profiles (anti-infectives).*
- *Pharmacologically active metabolites (relative contribution to pharmacodynamics).*
- *Immunological properties, including antigenic specificity for monoclonal antibodies.*

For antimicrobial medicinal products the mechanism of action, in vitro spectrum of activity including wild type distribution of MIC values (if available), post antibiotic effects and mechanism of resistance should be described. The in vivo efficacy in animal model by species of bacterium for example should be described. The PK/PD relationship established in animal model could be described here or under pharmacokinetics. The clinical section should cross-refer to this information.

For similar biological medicinal products:

A battery of receptor-binding studies or cell-based assays, (many of which may already be available from quality-related bioassays), are

normally a part of the comparability exercise in order to assess if any differences in reactivity are present and to determine the likely causative factor.

Animal studies are designed to maximise the information obtained and to compare reference and similar biological medicinal products intended to be used in the clinical trials. Such studies are performed in a species known to be relevant and employ state of the art technology.

Assessor's comment

2.2. Secondary pharmacodynamics

This section should describe pharmacological effects other than the primary therapeutic activity (previously general pharmacology).

Mention receptor screen(s) as appropriate.

For monoclonal antibodies, the immunological properties of the antibody other than those intended should be described here in detail, including complement binding and any unintentional reactivity and/or cytotoxicity towards human tissues distinct from the intended target. Such cross- reactivity studies can be carried out using a range of human tissues and should be described.

Assessor's comment

2.3. Safety pharmacology

The following points should be addressed: Core battery (GLP):

- *Cardiovascular system (including QT prolongation in-vitro/in-vivo)*
- *Central nervous system*
- *Respiratory system*

Other e.g. Renal and GI system

For similar biological medicinal products

Normally other routine toxicological studies such, as safety pharmacology studies are not required for similar biological

medicinal products, unless indicated of results of repeat dose studies

Assessor's comment

2.4. Pharmacodynamic drug interactions

Potential pharmacodynamic drug interactions may include:

- *Interactions at receptor level*
- *Possible co-medications in the clinical setting*
- *Alerts from safety pharmacology, PK/metabolism or toxicology studies*

Assessor's comment

2.5. Assessor's overall conclusions on pharmacology

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.

Summarise the salient results from the main pharmacology studies and discuss the relevance of the models used for the intended therapeutic indication.

Provide an overview of the salient secondary and safety pharmacology findings, emphasising those predicting potential adverse events in humans.

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 "non-clinical overview" in the submitted dossier and comment on the suitability of the SPC wording. 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, if relevant) and that all information in the SPC is explicitly assessed and supported by the scientific assessment.

3. Pharmacokinetics (CTD MODULES 2.6.4 AND 4.2.2)

- **Pharmacokinetic studies**

Brief overview of studies. See further toxicokinetic studies in repeat- dose toxicity.

Assessor's comment

3.1. Methods of analysis

The assessment report should contain a brief discussion on the methods of analysis and their validation. When used in toxicokinetic studies they should comply with GLP.

Units of measurement should be clearly defined (e.g. molarity or mg/ml) and the same units used consistently as much as possible.

The assessor should comment on the availability of this information and on any discrepancies between the studies.

Assessor's comment

3.2. Absorption

Points of discussion may include:

- *Site of absorption for oral preparations if possible (usually not known which GI segment(s) involved)*
- *Single and repeat dose kinetics*
- *Dose proportionality*

- *Gender differences if available*
- *Interspecies comparison (species used in toxicology studies and data in humans should be included)*
- *Absolute bioavailability*
- *Formation of neutralising antibodies (biotech products).*

Tabulation of the data may be a useful aid, including e.g. species, dose, route, Cmax, tmax, AUC, t½, Vd, Clt and F% (see example below).

Where the PK is linear, representative data are sufficient. Examples of tables to tabulate absorption data:

Study ID	Species	N	Dose (mg/kg)	Route	Anal.	Cmax ()	tmax ()	AUC ()
A								
B								

Study ID	Species	N	Dose (mg/kg)	Route	Anal.	t½, el ()	Vd ()	Clt ()	F (%)
A									
B									
Re a)									
Re b)									

Assessor's comment

3.3. Distribution

The following data should be considered:

- *Tissue distribution studies mention of method (e.g. autoradiography).*

- *Protein binding (albumin, other) in different species with estimation of the free fraction including humans.*
- *Distribution in blood cells if possible (not systematically done).*
- *Placental transfer studies.*
- *Melanin binding (specific study in pigmented rat!).*
- *Excretion in the milk should be highlighted.*

Discuss degree of distribution in relation to possible target organs for toxicity and tissue retention if applicable (especially if effects at site of retention).

Plasma protein binding should be considered. Data in humans should be included and interspecies comparison made. The need to compare free concentrations should be addressed.

If there are indications of melanin binding, the need for assessment of phototoxicity should be commented, considering e.g. degree of light absorption; possible DNA binding should be also considered.

Distribution of parent compounds vs metabolites to be discussed in this context as appropriate.

Assessor's comment

3.4. Metabolism

The following data should be considered under the following headings:

- *Chemical structures and quantities of metabolites in biological matrices (table).*
- *Possible metabolic pathways (add picture if available).*
- *Presystemic metabolism (GI/hepatic first-pass effects).*
- *In vitro metabolism, mainly P450 (microsomal) studies: affinity, substrate specificity for subfamilies, inhibition studies (if positive, type of inhibition: reversible, suicide), drug interactions (clinically relevant associations). Non-microsomal oxidations, reduction, hydrolysis if applicable.*
- *Enzyme induction.*
- *Phase II (conjugation) metabolism mainly in-vivo.*

It is important to compare metabolic patterns in animals and humans. Identify if there are species-specific metabolites, particularly if the animals used for safety testing do not form metabolites that have been identified in humans.

This is an important part of the assessment of the relevance of the animal models used.

Assessor's comment

3.5. Excretion

It may be useful to tabulate data (see example below). Comment on routes of excretion which could be of value for assessment of organ specific toxicity.

If there are major differences in excretion patterns (metabolites) between animal and human, the animal species may be of less relevance to assess toxicity related to respective excretion organ.

Data and comments on mass balance should be included. Example of a table to tabulate excretion data:

Species	N	Dose (mg/kg)	Route	Anal.	Urine (% dose)	Faeces (% dose)	Bile (% dose)	Recovery (% dose)	Time (h)
					±	±	±	±	±
					±	±	±	±	±

Assessor's comment

3.6. Pharmacokinetic drug interactions

Focus on interactions with drugs that are potentially going to be co-administered in the clinical situation.

3.7. Other pharmacokinetic studies

If relevant, use the following headings: Studies in juvenile animals

Studies in pregnant animals

Studies in animal models of disease

Assessor's comment

3.8. 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 a comprehensive access to the relevant findings thus enabling adequate benefit risk assessment

Give an overview of the salient pharmacokinetic features. Comment on the relevance of the animal species used in the toxicity testing for human safety assessment e.g. considering metabolic patterns. Other important aspects may include major differences in absorption/bioavailability, interindividual/interspecies variability, elimination rates (differences in t½), etc.

Comment on other issues that may be of importance for the safety assessment e.g. distribution to target organs, excretion routes, and pharmacologically active metabolites. Discuss interspecies differences and compare with the clinical situation.

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.

Ensure correspondence with SPC (particularly 5.3 Preclinical safety data but also e.g., sections 5.2 Pharmacokinetic properties, 4.3 contraindications, 4.5 Interactions, 4.6 Pregnancy and lactation, if relevant) and that all information in the SPC is explicitly assessed and supported by the scientific assessment.

4. Toxicology (CTD MODULES 2.6.6 AND 4.3.3)

4.1. Single dose toxicity

The duration of observation (14 days in a standard GLP study) and a short statement on whether studies revealed low or high acute toxicity should be included.

It is considered useful to include the approximate lethal dose or observed maximum non-lethal dose.

The clinical signs of acute toxicity (briefly) and the mode and time of death (early/same day or delayed).

Target organs, (histo)pathology if available. Example of a table for single dose toxicity studies:

Study ID	Species/ Sex/Number/ Group	Dose/Route	Approx. lethal dose / observed max non-lethal dose	Major findings

Assessor's comment

4.2. Repeat-dose toxicity

The pivotal studies should be organised by species and route of administration. Comment on GLP for overall programme and specify any deviations (e.g. contamination of controls).

A short description of the design (strain, route of administration, dose groups, number animals/gender/group, recovery groups if any, TK if performed).

The main findings should be comprehensively described, namely; death, body weight, relevant laboratory findings, target organs with type of histopathological lesions, dose-dependency, onset, severity, species or gender related differences and duration of toxic effect.

The No Observed Adverse Effect Level (NOAEL) in the different species should be provided (if established) with comments on the relation of the systemic exposure at that dose level to the systemic exposure in humans given the maximum intended dose (exposure margin).

A statement whether reversibility has been demonstrated in the recovery group should be included.

Comments on TK (linearity, gender dependency, accumulation).

The use of tables (example below) or figures could facilitate the comprehension of the largely descriptive tests.

Highlight the important findings; discuss the mechanistic background and the margin to the clinical exposure.

For similar biological medicinal products usually at least one repeat dose toxicity study, including toxicokinetic measurements has been conducted. Toxicokinetic measurements including determination of antibody titres, and cross reactivity and neutralizing capacity are part of this study. The studies allow detection of relevant differences

in toxicity and/or immune responses between similar biological medicinal product and reference product.

Normally other routine toxicological studies such reproduction toxicology, mutagenicity and carcinogenicity studies are not required for similar biological medicinal products, unless indicated from results of repeat dose studies.

Example of a table to show repeat-dose toxicity studies:

Study ID	Species/Sex/ Number/Group	Dose/Route	Duration	NOEL/ NOAEL (mg/kg/day)	Major findings

Assessor's comment

- **Toxicokinetics**

Analyses of plasma samples from control animals should be included.
Example of a table to show toxicokinetic studies:

Study ID	Daily Dose (/)	Animal AUC (ng.h/ml)		Animal:Human XXX Exposure Multiple	
		♂	♀	♂	♀

Assessor's comment

- **Interspecies comparison**

Example of a table to compare the exposure in the animal studies with the clinical exposure:

Study ID	Daily Dose (/)	Animal AUC (ng.h / ml)		Cmax		T ½	
		♂	♀	♂	♀	♂	♀

Assessor's comment

4.3. Genotoxicity

Provide an overview of the tests performed.

Sort the performed tests according to the 'level' of genotoxicity, i.e. mutagenicity (gene mutations), chromosomal aberrations (clastogenicity) in-vitro, chromosomal aberrations (clastogenicity) in- vivo, primary DNA damage and other genotoxic effects.

Preferably, present results in a table (see example below) and add comments if needed in the text below.

If there are no remarkable findings in the in-vitro tests, inclusion in the table is sufficient.

The relevance of the species used in the in-vivo tests as well as of the system used for metabolic activation (e.g. S9 fraction) in the in-vitro tests, based on comparisons with the metabolic pattern in humans should be commented on.

A statement on the exposure should always be included for the in-vivo tests (refer to toxicokinetics studies).

Example table of the overview of genotoxicity studies:

Type of test / study ID / GLP	Test system	Concentrations / Concentration range / Metabolising system	Results Positive / negative / equivocal
Gene mutations in bacteria	Salmonella strains	+/- S9	
Gene mutations in mammalian cells	CHO-cells, HGPRT-locus	+/- S9	
Chromosomal aberrations in vivo	Mouse, micronuclei in bone marrow	+/- S9	

Issues to consider when evaluating genotoxicity tests: For in-vitro tests:

- *Which strains /cells are used and which endpoints.*
- *Selection of concentrations.*
- *Stability in the medium (check of concentration/degradation products).*
- *Metabolising system.*
- *Positive and negative controls.*
- *Treatment time/sampling time.*
- *Criteria for positive response.*
- *Concentration-response relationship.*
- *Reproducibility.*
- *Cytotoxicity / cell survival.*

For in-vivo tests:

- *Which species/strain/model was used?*
- *Number and gender of animals.*
- *Doses and exposure.*
- *Exposure established by toxicity or kinetics.*
- *Metabolic differences between species and human.*
- *Treatment and sampling times.*
- *Applicant's criteria for positive response.*
- *Dose/time-response relationship.*

Example of a statement that can be used when summarising the genotoxicity test battery:

The genotoxicity of X has been studied with respect to gene mutations in bacteria and mammalian cells and chromosomal aberrations in-vitro and in-vivo. Additionally, tests of primary DNA damage in-vitro and malignant cell transformation have been conducted.

Issues to discuss:

- *Positive findings in either in-vitro or in-vivo tests.*
- *Mechanistic background: mutagenic or clastogenic.*
- *Is a threshold approach possible?*
- *If yes, what is the margin of safety with human plasma*

level/exposure?

- *Conclusions on the genotoxic potential.*

Assessor's comment

4.4. Carcinogenicity

5.4.1. Long-term studies

Give a short presentation of the studies that have been performed, preferably as a table under respective subheading, e.g. long-term studies; short-term, other etc (example below).

If carcinogenicity studies have not been performed the applicants' justification should be discussed.

Example table of the overview of carcinogenicity studies performed:

Give a short summary of results including neoplastic changes as well as relevant non-neoplastic changes, as appropriate. Non-neoplastic changes should be discussed with reference to the observations in repeat-dose toxicity studies. Preferably, list results in a Table (example below).

Example table of tumour findings in Study xx

Study ID /GLP	Dose / Route	Exposure (AUC)	Species / No. of animals	Major findings

Example table of tumour findings in Study xx:

Tumour findings	Control	Low dose	Mid dose	High dose
	Male			
	Female			

Issues to be considered in detail:

- *Species strain and gender.*
- *Number of groups (control groups).*
- *Number of animals per group.*

- *Route of administration*
- *Duration of treatment.*
- *Growth (BW gain and FC)*
- *Survival at the end of the study.*
- *Toxicokinetics (in a table: day of sampling, AUC,).Sampling of controls*
- *Tumour findings organs, type (B or Malignant), incidence.*
- *Pre-neoplastic findings.*
- *Nomenclature of tumours.*
- *Statistical methods used.*
- *Toxic findings not seen in the studies of shorter duration.*

Assessor's comment

5.4.2. Short or medium-term studies

New models:

- *Which models and the rationale for use.*
- *If genotoxicity under discussion.*
- *Number of animals and treatment period.*
- *Use of positive control and the response.*
- *Use of comparative compound (if applicable).*
- *Statistical analysis of most important tumours.*

Assessor's comment

5.4.3. Other studies

If present, e.g. mechanistic studies to explain a tumorigenic effect of the product or metabolite(s).

Assessor's comment

4.5. Reproductive and developmental toxicity

Give a summary presentation of the performed studies, preferably in a table (example below) including dose-finding studies, as appropriate.

Comment on GLP for each pivotal study. If the information contained in the table is not sufficient for a particular study, factual data may be further described under each specific heading below.

Consider information relevant to reproduction toxicity from other sections of the dossier, either as cross-reference or facts. For instance, histopathology of reproductive organs from repeat-dose toxicity, endocrine effects, pharmacokinetics, pharmacodynamics should be considered.

Example summary table of the performed studies:

Study type / Study ID / GLP	**Species; Number Female / group**	**Route & dose**	**Dosing period**	**Major findings**	**NOAEL (mg / kg &AUC)**
Male fertility					
Female fertility					
Embryo-fœtal development					F0
					F1
Peri & postnatal					

Assessor's comment

5.5.1. Fertility and early embryonic development

Assessor's comment

5.5.2. Embryo-fœtal development

Assessor's comment

5.5.3. Prenatal and postnatal development, including maternal function

Assessor's comment

5.4.4. Studies in which the offspring (juvenile animals) are dosed and/or further evaluated

Conclusions on the reproductive toxicity.

Comment on the relevance of the tested systems used (e.g. species/strain) (e.g. based on comparative metabolism and kinetics, comparative pharmacodynamics).

Evaluate exposure and distribution data in pregnant and/or lactating animals, and in offspring (including milk excretion).

Include critical assessment on each specific area of the studies and provide concluding remarks considering relevant findings.

Consider margins of exposure and assess the clinical relevance of the findings.

Provide suggestions and justifications for SPC recommendations.

4.6. Local tolerance

A short comment on whether the compound showed any evidence of local irritancy at the site of administration. Sensitisation studies (see IV.7.1, should be included if applicable (dermal route).

Assessor's comment

4.7. Other toxicity studies

Any such studies should be noted and findings commented upon.

Assessor's comment

5.7.1. Antigenicity

Antibody formation, sensitisation (guinea pig assay) where applicable.

In the particular case of similar biological medicinal products, emphasis shall be put on the assessment of the differences in immunogenecity between the reference and the biosimilar medicinal product. Any potential consequences for clinical efficacy and safety should be discussed here and further with clinical and quality assessor colleagues.

Assessor's comment

5.7.2. Immunotoxicity

When performed, specific immunotoxicity investigations (together with relevant findings in repeat dose toxicity) should rather be discussed here especially when clinical implications are suspected.

Such studies may include cell surface markers (immuno-histology or flow cytometry), functional tests (primary Ab formation to SRBC, NK activity, macrophagic function, delayed hypersensitivity, host resistance tests, complement activation etc…).

See also ICH S8 and CHMP guidance on repeat dose toxicity

Implications for immune suppression, autoimmune potential, hypersensitivity reactions, in humans, should be mentioned.

Assessor's comment

5.7.3. Dependence

In conjunction with pharmacodynamic studies/models (not done routinely in toxicology).

Assessor's comment

5.7.4. Metabolites

Specific studies for major human metabolites (or isomers) insufficiently present in animals.

Assessor's comment

5.7.5. Studies on impurities

Studies for qualification of impurities: single or repeat dose, genotoxicity, reproduction. See ICH guidelines

Assessor's comment

5.7.6. Other studies

If appropriate, e.g.: Phototoxicity

Includes dermal/ocular photoxicity (when relevant), photosensitisation, photo-genotoxicity and photo-carcinogenicity.

Possible need of such studies depends on photo-absorption/degradation, dermal/ocular use/exposure (see relevant CHMP guidance).

Molecular toxicology

Reactive metabolites (in-vitro covalent binding to proteins, lipids, nucleic acids). Possible implications for idiosyncratic reactions or autoimmune diseases.

- *Other mechanistic studies (mitochondrial toxicity, Hb reactivity etc…)*
- *-omics data*

Assessor's comment

4.8. Ecotoxicity / environmental risk assessment

(CTD Module 1.6)

Mandatory for all new applications

See relevant CHMP guidance (CHMP/SWP/4447/00)

The ERA section of the AR contains a detailed assessment of the data submitted in accordance with the current guideline (EMEA/CHMP/SWP/4447/00) with a summary of the main study results (see table below) and a conclusion on the potential risks to the environment and if necessary recommendation for mitigation measures. Standard sentences (see examples below) should be used as much as possible.

A table capturing available data comes with the conclusion for phase II 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.

The format of the table is provided below.

Table for the assessment report providing relevant endpoints of the environmental risk assessment of human pharmaceuticals.

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,		µg/L	> 0.01 threshold (Y/N)

literature)					
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

Assessor's comment

5.8.1. Conclusion

Choice of minimal standard sentences suggested for the CONCLUSION in the AR/EPAR.

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 exposureis 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.

[At the time of opinion:] The applicant commits to perform the following studies as follow-up measures: [list of tests to be performed]

4.9. Assessor's overall conclusions on toxicology

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 a comprehensive access to the relevant findings thus enabling adequate benefit risk assessment.

Any deviations from the toxicology programme as stated in the guidelines or from GLP or any absence of required studies should be commented upon.

If it is a bibliographical application or if bibliographical data are used as supportive information, it is particularly important to highlight this.

In general, the rationale for the selection of species/systems, duration and dose/concentrations used in the studies should be provided.

Explanations for the observed effects as well as statements pertaining to the potential relevance for the human use as suggested by the applicant should be commented and if possible concluded upon.

The implications of any differences in the chirality, chemical form, and impurity profile between the compound used in the non-clinical studies and the product to be marketed should be discussed.

Interspecies comparisons of metabolism and systemic exposure comparisons in animals and humans (AUC, Cmax, and other appropriate parameters) should be discussed and the limitations and utility of the non-clinical studies for prediction of potential adverse effects in humans highlighted.

The relevance of the animals in toxicity studies should also be discussed with respect to potential interspecies differences in pharmacology.

Special emphasis should be put on genotoxicity, carcinogenicity and reproductive and developmental toxicity findings. In case of positive genotoxic effects, tumour findings and/or developmental/reproductive toxicity findings, the possible relevance for the human situation should be discussed and if possible concluded upon.

For the carcinogenicity potential consider:

Biological significance of tumour increases, historical data, relation to pharmacological effect, dose-related effects, species-specific differences, mechanistic studies, relationship with genotoxicity and comparison between human and animal exposure 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.

Please indicate if additional expertise is needed to assess the human implications. This includes whether there is a need to obtain an Opinion from the PDCO related to data with relevance to the paediatric development.

Comment on the suitability of the SPC wording. 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, if relevant) and that all information in the SPC is explicitly assessed and supported by the scientific assessment.

For similar biological medicinal products the similarity / differences in response between the similar biological product and the reference product and not just the response per se is discussed.

5.9.1. Implications of the assessment of non-clinical data for the Safety Specification of the Risk Management Plan (RMP)

(to be filled in by the CHMP rapporteur only)

[Paste in the Summary table of important non-clinical findings from module SII of the RMP. Comment on whether it adequately reflects the main non-clinical data, and whether changes are needed to be made by the Applicant.

Comment if non-clinical safety findings have been identified which may be of significant clinical relevance. Refer to the Overall conclusion on Toxicology (section 4.9) above; there is no need to repeat the discussion from that section.

In conjunction with the assessment of clinical data, it should be determined whether any findings should be included in the Safety Concerns of the RMP i.e. if there are findings that for humans can be considered as Important identified risks, Important potential risks or as Missing Information. 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).

Examples of non-clinical findings that might be included in the Safety Specification are more serious reproductive toxicity, leading to strict recommendations regarding use in pregnancy/women of child bearing potential, serious findings in carcinogenicity studies where human relevance cannot be excluded, genotoxic potential, or serious findings in repeat dose toxicity studies, which may be of significant relevance for human safety.

5. List of references

6. List of questions 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. Other concerns should be resolved before approval; failure to do so may render the application un-approvable.

This list should be carried forward to the "overview module".

Non-clinical aspects

Major objections

Pharmacology

Pharmacokinetics

Toxicology

Other concerns

Pharmacology

Pharmacokinetics

Toxicology

7. 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).

More general comments could also be made here.