DECISION

No. 27/01.11.2010

on approval of the Guideline for elaboration of non-clinical documentation assessment report

The Scientific Council of the National Agency for Medicines and Medical Devices,

set up based on Order of the Minister of Health No. 1123/18.08.2010, reunited on summons of the NAMMD President in the ordinary meeting of 01.11.2010, in accordance with Article 12(5) of Government Decision No. 734/2010 related to the organisation and operation of the National Agency for Medicines and Medical Devices, as amended, agrees on the following

DECISION

Art. 1. - The Guideline for elaboration of non-clinical documentation assessment report, is approved according to the Annex which is integral part of this decision.

Art. 2. - On the date of the coming into force of this Decision, NMA Scientific Council Decision No. 20/22.05.2006 on approval of the Guideline for elaboration of non-clinical documentation assessment report is repealed.

PRESIDENT
of the Scientific Council
of the National Agency for Medicines and Medical Devices,
Acad. Prof. Dr. Leonida Gherasim

ANNEX

GUIDELINE

for elaboration of non-clinical documentation assessment report

GENERAL GUIDANCE

Art. 1. – (1) This Guideline is a translation into Romanian and an adaptation of EMEA Guideline *CHMP Day 80 Critical Assessment Report Non-clinical (Non-clinical assessment report starting from Day 80).*

(2) The Guideline may be used for assessment of documentation submitted as both "Common Technical Document" (CTD) format and eCTD format.

(3) It provides recommendations related to the set up of the non-clinical documentation assessment report.

Art. 2. - The report should be sufficiently detailed to allow for secondary assessment by other assessors.

Art. 3. – (1) The report should describe salient findings and especially those deficiencies that justify the questions intended for the applicant.

(2) These questions will also be listed in the "Overview module" of the assessment.

Art. 4. - 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), as well as references to the literature or other sources.

Art. 5. – (1) Critical assessment (e.g. comments on the data validity and interpretation, conclusions) should be described in the "Assessor's comments" sub-sections that follow each chapter.

(2) The words "Major objections" may be used when necessary (see List of findings/questions/objections as proposed by the Rapporteur).

Art. 6. - 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).

Art. 7. - The report should also emphasise findings that need to be reflected in the Summary of Product Characteristics (SPC).

Art. 8. – (1) 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 in yellow.

(2) These sections will be removed before the Public Assessment Report (PAR) is sent to the applicant.

Art. 9. - (1) The use of tables/graphs/figures is encouraged; examples are given in the template and are to be used as appropriate.

(2) PK/TK tables (pharmacokinetics/toxicokinetics) should include the number of animals and standard deviation for each parameter.

(3) For repeat-dose studies, TK day of sampling should be mentioned.

(4) Tables taken from the dossier may also be included into the assessment.

(5) Footnotes should also be considered.

Art. 10 - 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.

Art. 11. - It is recommended that the font used in the main text be Times New Roman, size 11.

Art. 12. - See specific CHMP or CHMP/ICH Notes for guidance as a general framework for guidance: http://www.emea.eu.int/index/indexhl.htm

Art. 13. – Likewise, the CTD guidance text should be taken into account.

NON-CLINICAL CRITICAL ASSESSMENT

CHAPTER I
INTRODUCTION

I.1 Type of application for marketing authorisation and aspects of medicinal product development

Type of application

Art. 14. - (1) Indicate type of marketing authorisation application (reference to the legal basis of the application), e.g. bibliographic, mixed, products with well-established use, biosimilars etc. and if acceptable justifications exist for waiving certain studies or replacing original studies by literature data.

(2) 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.

Art. 15. - (1) For each main section of the assessment report for modules 4 and 5, the report should describe the data submitted in accordance with Analytical, pharmacotoxicological and clinical norms and protocols in respect of the testing of medicinal products, approved through Order of the Minister of Health No. 615/01.06.2010, transposing Annex 1 to Directive 2001/83.

(2) The types of studies addressed within each section should include all indents as listed in Analytical, pharmacotoxicological and clinical norms and protocols in respect of the testing of medicinal products.

(3) 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.

Art. 16. - 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.

Art. 17. – (1) Where the data submitted deviate from the requirements, the acceptability of any justifications should be assessed.

(2) 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.

Art. 18. - 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 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 unethical1-2, or the conduct of certain animal tests is considered to lead to unnecessary use of animals1, 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 upon the final benefit/risk assessment.
The applicant is unable to provide comprehensive data on the efficacy and safety of the product under normal conditions of use ("exceptional circumstances").	Under extraordinary circumstances, 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, amended and the guideline on the granting of a marketing authorisation under extraordinary circumstances, in accordance with Art. 14(8) of Regulation (EC) No. 726/2004).

1-2 - Requirements of GCP principles of Directive 2001/20/EC and Directive 2001/83/EC as amended by Directive 2001/20/EC (Declaration of Helsinki also provides a useful reference).

1 - Directive EC 86/609/CEE on Animal Welfare and Council Decision on the European Convention of the Protection of Vertebrae Animals.

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

- Council Directive 86/609/EEC on the protection of animals and Council Decision related to the European Convention for the Protection of Vertebrate Animals.

Aspects of medicinal product development

Art. 19. - (1) Introduce and comment on the clinical development programme in view of the proposed indication(s) and posologies (Indicate availability of paediatric indication or any paediatric development).

(2) Mention whether the types of studies are compliant with EU/ICH guidelines. (e.g. M3 – Guideline on Nonclinical Safety Studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals, S6 – Guideline on the preclinical safety evaluation of biotechnology –derived pharmaceuticals).

Art. 20. - State whether the applicant has requested an accelerated assessment and whether relevant criteria are met.

Art. 21. – (1) In the particular case of a "biocomparability exercise", the development strategy chosen by the manufacturer, justified and assessed in accordance with relevant guidelines is described.

(2) In case of similar biological products, relevant guidelines should be taken into account (EMEA/CHMP/437/04 Guideline on Similar biological medicinal products, EMEA/CHMP/42832/2005 Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues and the annexes specific to the respective medicinal product attached to this guideline, and EMEA/CHMP/BWP/49348/05 Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues).

(3) In view of assessing the similarity of the quality, safety and efficacy profile of similar biological medicinal products and reference medicinal products already authorised in the Community, an extended comparability exercise is required.

(4) Detailed information on the reference medicinal product (commercial name), strength, pharmaceutical form, Marketing Authorisation Holder, date of authorisation in the EU and detailed information (e.g. manufacturing series and country of origin) on the series used in the comparability exercise (quality, non-clinical, clinical) should be provided in tabulated format in the section of the report related to quality.

Art. 22. – (1) It shall be specified whether an agreement has been reached with the PDCO (Paediatric Committee) concerning a Paediatric Investigation Plan (with or without delay) or if the medicinal product was applied a specific class derogation.

(2) A summary of the conditions and main requirements related to non-clinical issues of the paediatric investigation plan shall be presented, if required, and the relevant key-information related to the actual situation of non-clinical studies (if accomplished, in-process etc.) shall be stated.

Art. 23. – State when and if scientific counselling/assistance has been granted in view of setting up the protocol. The issues shall be stated and it shall be mentioned whether the recommendation has been followed by the applicant.

Art. 24. – If other batches of medicinal products than those meant for marketing have been used in part of the studies, the qualification of the new impurities should be assessed (if any).

I.2 Good Laboratory Practice (GLP) aspects

Art. 25. - Statements on GLP should be addressed here and also in the "overview module" of the assessment.

Art. 26. – This section shall specifically state the following:

- Any doubts having occurred during the assessment of the compliance with GLP requirements (accuracy of data or compliance with the protocol).
- The need for a GLP inspection shall be discussed.

Art. 27. – The following are required in view of requesting a GLP inspection:

- To contact the Pharmaceutical Inspection Department, in view of GLP inspection coordination.
- To establish by joint agreement, the studies, sites of conduct and main grounds for worrying or inspection issues.

CHAPTER II
PHARMACOLOGY (CTD, MODULES 2.6.2 and 4.2.1)

- **Brief summary**

Art. 28. - (1) The active substance, manner of action and a brief justification of the product's development shall be presented for the proposed indication(s).

(2) In case of similar biological products, this section should highlight the comparative nature of the studies and justify the nonclinical development program. (The discussion over results may be included in the section „Discussion" in the end of the section.)

- **Physico-chemical data**

Art. 29. – Structure of the active substance (insert structure).

- Marking site (see structure)
- Isomerism
- Molecular weight
- Solubility in water
- Pka
- Distribution coefficient
- Solubility in other solvents
- Stability
- Possible chirality and its consequences

II.1 Primary pharmacodynamics

Art. 30. - This section should address pharmacodynamics (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 assays) including the species used in toxicology studies.
- Preliminary PK (plasma concentration) in animal models if available.
- Duration/reversibility of effects, resistance profiles (for anti-infectives).
- Pharmacologically active metabolites (relative contribution to pharmacodynamics).
- Immunological properties, including antigenic specificity for monoclonal antibodies.

Art. 31. - (1) As far as antimicrobials are concerned, the mechanism of action, *in vitro* action spectrum, including the distribution of MIC (minimum inhibitory concentration) values of the savage type (if available), the post-antibiotic effect and resistance mechanism should be described.

(2) E.g. The efficacy of *in vivo* species of bacteria on animal models should be described.

(3) The PK/PD relationship established on animal models could be described here or in the pharmacokinetics-related section; the clinical section should contain cross-reference to this.

<u>For similar biological medicinal products</u>

Art. 32. - (1) Normally, the comparability exercise needed in view of assessment of the presence of various reactivity differences and in view of establishing the potential causative factor contains a battery of receptor-binding studies or cell-based tests (many of which can already be available from quality-related biotests).

(2) Studies on animals are otherwise projective so as to maximize the pooled information and compare the medicinal and similar biological products meant for use in clinical trials.

(3) Such studies are performed on species known as relevant and employ the latest technologies.

II.2 Secondary pharmacodynamics

Art. 33. - (1) This section should describe pharmacological effects other than the primary therapeutic activity (previously called general pharmacology).

(2) Mention receptor screen(s) as appropriate.

(3) 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.

(4) Such cross-reactivity studies can be carried out using a range of human tissues and should be described.

II.3 Safety pharmacology

Art. 34. - The following points should be addressed in this section:

a) Core battery (GLP), related to the following:

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

b) Other systems, e.g. renal and gastrointestinal system.

For similar biological medicinal products

Art. 35. - Normally, similar biological products do not require other routine toxicological studies such as safety pharmacology studies, except for the case in which these are specified by the toxicity studies after repeated doses.

II.4 Pharmacodynamic drug interactions

Art. 36. - Potential pharmacodynamic drug interactions may include:

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

II.5 Assessor's overall conclusions on pharmacology

Art. 37. - (1) The content of this paragraph could be included in the „Overview" module of the evaluation.

(2) Due to this cause, a focused, individual elaboration could be required in order to allow the reader full access to relevant results.

Art. 38. – Summarise the salient results from the main pharmacology studies and discuss the relevance of the models used for the intended therapeutic indication.

Art. 39. – Provide an overview of the salient secondary and safety pharmacology findings, emphasising those predicting potential adverse events in humans.

Art. 40. – As an alternative, this section could simply state the main conclusions; in this case, section „Overview" should be elaborated separately.

Art. 41. – Highlight any areas of agreement/disagreement with the "non clinical overview" in the submitted dossier and comment on the suitability of the SPC wording.

CHAPTER III

PHARMACOKINETICS (CTD, MODULES 2.6.4 and 4.2.2)

• Pharmacokinetic studies

Art. 42. – Brief overview of the studies; see additional toxicokinetic studies in the context of toxicity following repeated doses.

III.1 Methods of analysis

Art. 43. – (1) The assessment report should contain a brief discussion on the methods of analysis and their validation.

(2) When used in toxicokinetic studies they should comply with GLP provisions.

Art. 44. - Units of measurement should be clearly defined (e.g. molarity or mg/ml) and the same units used consistently as much as possible.

Art. 45. - The assessor should comment on the availability of this information and on any discrepancies between the studies.

III.2 Absorption

Art. 46. - Points of discussion in this section may include:

- Site of absorption for oral preparations if possible (usually not known which gastrointestinal segment(s) is/are involved.
- Single and repeat dose kinetics
- Dose proportionality
- Data on gender differences if available
- Interspecies comparison (species used in toxicology studies and data in humans should be included)
- Absolute bioavailability
- Formation of neutralising antibodies (for biotechnology products)

Art. 47. - Tabulation of the data may be a useful aid, including e.g. species, dose, route of administration, Cmax, tmax, AUC, t½, Vd, Clt and F% (see the example below).

Art. 48. - Where the PK is linear, representative data are sufficient.

Art. 49. - Examples of tables to tabulate absorption data

Study ID	Species used	Number of animals used	Dose (mg/kg)	Administration route	Analytic assays	C_{max} ()	T_{max} ()	AUC ()
A B								

Study ID	Species used	Number of animals used	Dose (mg/kg)	Administration route	Analytic assays	$t_{½}$ elim ()	Vd ()	C_{lt} ()	F (%)
A B									
Re a)									
Re b)									

III.3 Distribution

Art. 50. - The following data should be considered and commented upon:

- 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).
- Placental transfer studies.
- Melanin binding (specific study in pigmented rat).
- Excretion in the milk should be highlighted.

Art. 51. – Discuss degree of distribution in relation to possible target organs for toxicity and tissue retention if applicable (especially if effects at site of retention).

Art. 52. – (1) Plasma protein binding should be considered. Data in humans should be included and interspecies comparison made.

(2) The need to compare free concentrations should be addressed.

Art. 53. – (1) If there are indications of melanin binding, the need for assessment of phototoxicity should be commented, considering e.g. degree of light absorption;

(2) possible DNA binding should be also considered.

Art. 54. - Distribution of parent compounds vs. metabolites to be discussed in this context as appropriate.

III.4 Metabolism

Art. 55. - 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 (gastrointestinal/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.

Art. 56. - It is important to compare metabolic patterns in animals and humans.

Art. 57. - 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.

Art. 58. - This is an important part of the assessment of the relevance of the animal models used.

III.5 Excretion

Art. 59. – (1) Data should be tabulated (see example below).

(2) Comment on routes of excretion which could be of value for assessment of organ specific toxicity.

Art. 60. - 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.

Art. 61. - Data and comments on mass balance should be included.

Art. 62. - Example of a table to tabulate excretion data:

Species used	Numbers of animals used	Dose (mg/kg)	Administration route	Analytical assay	Urine (% dose)	Faeces (% dose)	Bile % dose)	Recovery (% dose)	Time (hours)
					±	±	±	±	±
					±	±	±	±	±

III.6 Pharmacokinetic drug interactions

Art. 63. - Focus on interactions with drugs that are potentially going to be co-administered in the clinical situation.

III.7 Other pharmacokinetic studies

Art. 64. - If relevant, use the following headings:

- Studies in juvenile animals
- Studies in pregnant animals
- Studies in animal models of disease

III.8 Assessor's overall conclusions on pharmacokinetics

Art. 65. – (1) Give an overview of the salient pharmacokinetic features.

(2) Therefore, a focused and independent elaboration could be required, so as to grant readers full access to relevant results, thus ensuring an adequate risk-benefit assessment.

Art. 66. – (1) The main pharmacokinetic features shall be reviewed.

(2) Comment on the relevance of the animal species used in the toxicity testing for human safety assessment e.g. considering metabolic patterns.

(3) Other important aspects may include major differences in absorption/bioavailability, inter-individual/interspecies variability, elimination rates (differences in t½) etc.

Art. 67. – (1) 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.

(2) Discuss interspecies differences and compare with the clinical situation.

Art. 68. – As an alternative, this section could simply state main conclusions; in this case, the text of the module „Overview" should be elaborated separately.

CHAPTER IV
TOXICOLOGY (CTD, MODULES 2.6.6 and 4.3.3)

IV.1 Single dose toxicity

Art. 69. - 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.

Art. 70. - It is considered useful to include the approximate lethal dose or observed maximum non-lethal dose.

Art. 71. - The clinical signs of acute toxicity (briefly) and the mode and time of death (early/same day or delayed).

Art.72. - Target organs, (histo)pathological changes, if available.

Art. 73. - Example of a table for single dose toxicity studies:

Study ID	Species/gender/number of animals used/group	Dose/administration route	Approx. lethal dose/observed max. non-lethal dose	Major findings

IV.2 Repeat-dose toxicity

Art. 74. – (1) The pivotal studies should be organised by species and route of administration.

(2) Comment on GLP for overall programme and specify any deviations (e.g. contamination of controls).

Art. 75. - A short description of the design (strain, route of administration, dose groups, number of animals/gender/group, recovery groups if any, TK) if performed.

Art. 76. - 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.

Art. 77. - 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).

Art. 78. - A statement whether reversibility has been demonstrated in the recovery group should be included.

Art. 79. - Comments are made on TK (linearity, gender dependency, accumulation).

Art. 80. - The use of tables (see examples below) or figures could facilitate the comprehension of the largely descriptive tests.

Art. 81. - Highlight the important findings; discuss the mechanistic background and the margin to the clinical exposure.

Art. 82. – (1) **As regards similar biological products,** at least one toxicity study after repeated dose is usually performed, including toxicokinetic measures.

(2) Toxicokinetic measures, among which the determination of antibody titers, cross-reactivity and neutralising capacity are included in this study.

(3) Studies allow the detection of relevant differences in immune answers and/or toxicity between similar biological medicinal products and the reference product.

Art. 83. – Generally speaking, similar biological medicinal products do not require other routine toxicological studies, such as toxicity studies on reproduction, mutagenicity and carcinogenicity, except for the case when this fact is indicated by study results following repeated doses.

Art. 84. - Example of a table to show repeat-dose toxicity studies:

Study ID	Species/gender/number of animals used/group	Dose/Administration route	Study duration	NOEL/NOAEL (mg/kg/day)	Major findings

- **Toxicokinetics**

Art. 85. - Analyses of plasma samples from control animals should be included.

Art. 86. - Example of a table to show toxicokinetic studies:

Study ID	Daily dose (/)	Animal AUC (ng x. hour/ml)	Animal/Human Exposure Multiple
		♂ ♀	♂ ♀

- Preferably free AUC values should be used for comparison.

- **Interspecies comparison**

Art. 87. - Example of a table to compare the exposure in the animal studies with the clinical exposure:

Study ID	Daily dose (/)	Animal AUC (ng x. hour/ml)	C_{max}	t ½
		♂ ♀	♂ ♀	♂ ♀

IV.3 Genotoxicity

Art. 88. - Provide an overview of the tests performed.

Art. 89. - 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.

Art. 90. - Preferably, present results in a table (see example below) and add comments if needed in the text below.

Art. 91. - If there are no remarkable findings in the *in-vitro* tests, inclusion in the table is sufficient.

Art. 92. - 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.

Art. 93. - A statement on the exposure should always be included for the *in-vivo* tests (refer to toxicokinetics studies).

Art. 94. - 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 Gene mutations in mammalian cells Chromosomal aberrations *in- vivo*	*Salmonella* strains CHO-cells, *HGPRT-locus* Mouse, micronuclei in bone marrow	±S9 ±S9 mg/kg	

Art. 95. - Issues to consider when evaluating genotoxicity tests:

a) For *in-vitro* tests:

- Which strains/cells are used and which endpoints?
- Selection of concentrations used
- 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

b) For *in-vivo* tests:

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

Art. 96. - Example of a statement that can be used when summarising the genotoxicity test battery may be as follows:

"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".

Art. 97. – The following issues are to discuss:

- Positive findings in both *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

IV.4 Carcinogenicity (Carcinogenic potential)

IV.4.1 Long-term studies

Art. 98. – 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.

Art. 99. - If carcinogenicity studies have not been performed, the applicants' justification should be discussed.

Art. 100. - Example table of the overview of carcinogenicity studies performed:

Type of test/GLP	Dose/administration route	Exposure (AUC)	Species/number of animals used	Major findings

Art. 101. – (1) Give a short summary of results including neoplasic changes as well as relevant non-neoplasic changes, as appropriate.

(2) Non-neoplasic changes should be discussed with reference to the observations in repeat-dose toxicity studies.

(3) Preferably, list results in a table (example below).

Art. 102. - Example table of tumour findings in Study XXX:

Tumour findings	Control	Low dose	Mid dose	High dose
	Males Females			

Art. 103. – issues to be considered in detail:

- Species strain and gender;
- Number of groups (control groups included);
- Number of animals used per group;
    - route of administration;
    - duration of treatment;
    - growth (weight curve and food intake);
    - survival at the end of the study;
- Toxicokinetics (in a table: day of sampling, AUC);
- Tumour findings in organs, type (B or Malignant), incidence;
    - pre-neoplasic findings;
    - nomenclature of tumours;
    - statistical methods used;
    - Toxic findings not seen in the studies of shorter duration.

IV.4.2 Short or medium-term studies

Art. 104. – In case new models are used:

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

IV.4.3 Other studies

Art. 105. - This section applies if other studies have been performed, for instance mechanistic studies to explain a tumorigenic effect of the product or metabolite(s).

IV.5 Reproductive and developmental toxicity

Art. 106. - Give a summary presentation of the performed studies, preferably in a table (example below) including dose-finding studies, as appropriate.

Art. 107. – (1) Comment on GLP for each pivotal study.

(2) 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.

Art. 108. – (1) Consider information relevant to reproduction toxicity from other sections of the dossier, either as cross-reference or facts.

(2) For instance, histopathology of reproductive organs from repeat-dose toxicity, endocrine effects, pharmacokinetics, pharmacodynamics should be considered.

Art. 109. - Example summary table of the performed studies:

Type of test/GLP	Species/ number of females/ group	Administration route and dose	Dosing period	Major findings	NOAEL (mg/kg & AUC)
Fertility in Males Fertility in females Embryo-foetal development Prenatal and postnatal development					 F0 F1

IV.5.1 Fertility and early embryonic development

Art. 110. – Assessor's comments are included.

IV.5.2 Embryo-foetal development

Art. 111. - Assessor's comments are included.

IV.5.3 Prenatal and postnatal development, including maternal function

Art. 112. - Assessor's comments are included.

IV.5.4 <u>Studies in which the offspring (juvenile animals) receive medicinal products or are further evaluated</u>

Art. 113. - Conclusions on the reproductive toxicity are drawn.

Art. 114. - Comment on the relevance of the tested systems used (e.g. species/strain) (e.g. based on comparative metabolism and kinetics, comparative pharmacodynamics).

Art. 115. - Evaluate exposure and distribution data in pregnant and/or lactating animals, and in offspring (including milk excretion).

Art. 116. - Include critical assessment on each specific area of the studies and provide concluding remarks considering relevant findings.

Art. 117. - Consider margins of exposure and assess the clinical relevance of the findings.

Art. 118. - Provide suggestions and justifications for SPC recommendations.

IV.6 Local tolerance

Art. 119. - A short comment on whether the compound showed any evidence of local irritancy at the site of administration. Sensitisation studies should be included if applicable (see IV. 7. 1.) - dermal route.

IV.7 Other toxicity studies

Art. 120. - Any such studies should be noted and findings commented upon.

IV.7.1 Antigenicity

Art. 121. - Antibody formation, sensitisation (guinea pig assay) where applicable.

Art. 122. – (1) In the particular case of similar biological medicinal products, emphasis shall be put on the assessment of the differences in immunogenicity between the reference and the biosimilar medicinal product.

(2) Any potential consequences for clinical efficacy and safety should be discussed here and further with clinical and quality assessors.

IV.7.2 Immunotoxicity

Art. 123. - When performed, specific immunotoxicity investigations (together with relevant findings in repeat dose toxicity) should rather be discussed here especially when clinical implications are suspected.

Art. 124. - 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.).

Art. 125. - See also CHMP guidance on repeat dose toxicity.

Art. 126. - Implications for immune suppression, autoimmune potential, hypersensitivity reactions, in humans, should be mentioned.

IV.7.3 Dependence

Art. 127. - In conjunction with pharmacodynamic studies/models (not done routinely in toxicology).

IV.7.4 Metabolites

Art. 128. - Specific studies for major human metabolites (or isomers) insufficiently present in animals.

IV.7.5 Studies on impurities

Art. 129. - Studies for qualification of impurities after single or repeat dose, genotoxicity, reproduction. See ICH guidelines.

IV.7.6 Other studies

Art. 130. - If appropriate, the following should be assessed:

Phototoxicity

Art. 131. – (1) Includes dermal/ocular phototoxicity (when relevant), photosensitisation, photo-genotoxicity and photo-carcinogenicity.

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

Molecular toxicology

Art. 132. – Includes:

- Reagent 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 (toxicogenomics, transcriptomics, metabolomics, proteomics).

IV.8 Ecotoxicity/environmental risk assessment

Art. 133. – See relevant documentation in the CTD, module 1.6.

Art. 134. – (1) Mandatory for all new marketing authorisation applications.

(2) The Guideline on the environmental risk assessment of medicinal products for human use, approved through SCD No. 28/01.11.2011 (translation and adaptation of CHMP/SWP/4447/00 Guideline shall be consulted.

Art. 135. – (1) The section related to the environmental risk assessment of medicinal products for human use contains a detailed evaluation of the data provided in accordance with the Guideline on the environmental risk assessment of medicinal products for human use, a summary of the main studies' results (see the table below) and a conclusion concerning potential environmental risks, as well as the needed recommendations concerning the measures to be taken in view of diminishing the effects.

(2) Standard statements should be used as frequently as possible (see examples listed in 4.8.1 Conclusions).

Art. 136. – (1) Conclusions for assessment stage II are accompanied by a table containing available data.

(2) This table shall only contain the reliable/accepted results.

(3) Where there isn't any data, neither accepted nor required, the respective row should be deleted; this is a draft of the respective table.

Art. 137. – Table concerning the assessment report providing the final relevant criteria for the assessment of the risk of medicinal products' impact upon the environment.

Substance (INN/International Non-proprietary Name):
CAS number (if any):

PBT screening		**Outcome**	**Conclusions**
Bioaccumulation potential – log K_{ow}	OECD107 or…		PBT potential (Yes/No)
PBT assessment			
Parameter	**Relevant outcomes to conclusions**		**Conclusions**
Bioaccumulation	log K_{ow}		B/no B
	BCF		B/no B
Persistence	DT_{50} or rapidly biodegradable		P/no P
Toxicity	NOEC or CMR		T/no T
PBT statement:	The compound is neither a PBT, nor a vPvB The compound is a vPvB The compound is a PBT		

Phase I

Calculation	**Value**	**Measurement unit**	**Conclusions**
$PEC_{SURFACEWATER}$, (determined by prevalence, literature data)		µg/l	>0.01 threshold (Yes/No)
Other concerns (e.g. chemical class)			Yes/No

Phase II Physico-chemical properties and evolution of the substance in the environment

Study type	**Test protocol**	**Results**	**Comments**
Adsorption-Desorption	OECD 106 or…	K_{oc}=	List of all values
Rapid biodegradability assay	OECD 301		
Aerobic and anaerobic transformation in aquatic sediment	OECD 308	$DT_{50,}$water = $DT_{50,}$sediment = $DT_{50,}$ whole system = % sediment migration =	Not required, if slightly biodegradable

Phase IIA effect studies

Study type	Test protocol	Final criterion	Value	Units	Comments
Algae, growth inhibition test/Species	OECD 201	NOEC		µg/l	species
Daphnia sp., reproduction test	OECD 211	NOEC		µg/l	
Fish, toxicity test during the first stages of life/Species	OECD 210	NOEC		µg/l	species
Microorganism respiration inhibition test in an activated sediment	OECD 209	EC		µg/l	

Phase IIB recommended studies					
Bioaccumulation	OECD 305	BCF		l/kg	lipids %:
Ground aerobic and anaerobic transformation	OECD 307	DT_{50} CO_2 %			For all 4 types of solution
Ground microorganisms: nitrogen transformation test	OECD 216	effect %		mg/kg	
Ground plants, growing test/Species	OECD 208	NOEC		mg/kg	
Ground worms, acute toxicity tests	OECD 207	NOEC		mg/kg	
Collembolan reproduction test	ISO 11267	NOEC		mg/kg	
Organisms that live in the sediment		NOEC		mg/kg	species

IV.8.1 Conclusions

Art. 138. – The selection of minimal standard statements suggested for CONCLUSIONS in the assessment report.

Art. 139. – For active substances exempt for assessment in accordance with the guideline (vitamins, electrolytes etc.):

< The active substance is a natural substance, whose use shall not modify the substance's strength/release into the environment. Thus, the fact that <active substance> *could be hazardous at all for the environment is not foreseen.*

Art. 140. – For substances with PBT potential (persistent, bioaccumulative and toxic) and/or vPvB (highly persistent, highly bioaccumulative) or posing a specific risk (e.g. endocrine disrupters), the outcome of a specific assessment is added to standard conclusions, on a case-by-case basis.

Art. 141. – For active substances in Stage I:

The value of $PEC_{SURFACE\ WATER}$ (*Predicted Environmental Concentration) for* <active substance> *is below the action limit of 0.01 µg/l and is not a PBT substance as long as log* K_{ow} *does not surpass 4.5.*

Or for substances already marketed:

<The active substance> is already used in the marketed medicinal products and no significant raise of the exposure to the environment is foreseen. (on ground of justification).

Thus, the fact that the <active substance> is hazardous to the environment is not foreseen.

Art. 142. – For active substance in Phase II (see table):

The <active substance> is not a PBT substance, or if it is, a specific conclusion corresponding to PBT assessment shall be added.

- Taking into account the aforementioned data, it is not expected for the <active substance> to pose any risk for the environment.

- Taking into account the aforementioned data, the <active substance> should be used in accordance with the precautions stated in the SmPC in view of minimizing any potential environmental risk.

Art. 143. – For dossiers requiring extra data:

As a consequence to the aforementioned considerations, the available data do not allow a definitive conclusion concerning the potential risk posed by the < active substance> to the environment.

The applicant undertakes to conduct the following trials as follow-up measures: <list of tests to be carried out >

IV.9 Assessor's overall conclusions on toxicology

Art. 144. – The content of this paragraph can be included in the „Overview" of the section on assessment.

Art. 145. - A focused, individual elaboration could be required in view of granting full access to relevant results and an adequate assessment of the risk-benefit balance for the reader.

Art. 146. - Any deviations from the toxicology programme as stated in the guidelines or from GLP or any absence of required studies should be commented upon.

Art. 147. - If it is a bibliographical application or if bibliographical data are used as supportive information, it is particularly important to highlight this.

Art. 148. - In general, the justification for the selection of species/systems, duration and dose/concentrations used in the studies should be provided.

Art. 149. - 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.

Art. 150. - 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.

Art. 151. – Interspecies comparisons of metabolism and systemic exposure comparisons in animals and humans (AUC, C_{max}, 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.

Art. 152. - The relevance of the animals in toxicity studies should also be discussed with respect to potential interspecies differences in pharmacology.

Art. 153. – (1) Special emphasis should be put on genotoxicity, carcinogenicity and reproductive and developmental toxicity findings.

(2) 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.

Art. 154. – (1) 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.

(2) As an alternative this section could simply state the main conclusions, so that the "Overview" module should be elaborated separately.

Art. 155. – (1) Assessors should indicate if additional expertise is needed to assess the human implications.

(2) This includes the need for obtaining an Opinion of the PDCO (the Paediatric Committee for medicinal products for paediatric use) concerning relevant data for paediatric development.

Art. 156. – (1) Comments should be provided on the suitability of the SPC wording.

(2) Correspondence with the SPC is ensured (especially in section 5.3 Safety preclinical data, but also in section 4.3 Contraindications, in section 4.5 Interaction with other medicinal products and other types of interaction, section 4.6 Pregnancy and breastfeeding, if required).

Art. 157. – As far as similar biological products are concerned, answering similarities/differences shall be discussed for the similar biological product and for the reference product, not only the response *per se*.

CHAPTER V

LIST OF NON-COMPLIANCES/QUESTIONS/OBJECTIONS PROPOSED BY THE RAPPORTEUR

Definition of questions:

Art. 158. – (1) **"Major objections**", preclude a recommendation for marketing authorisation.

(2) In principle, one major objection may entail more than one question and the use of bullet points or subheadings is encouraged.

(3) It is vital that the structure and content of a major objection are clear and understandable to the reader.

(4) Detailed comments may be necessary along with a reference to guidance documents.

Art. 159. - Ideally, the objection should include a clarification as to what kind of response/action is expected from the applicant.

Art. 160. – (1) "**Other concerns**", may affect the proposed conditions for marketing authorisation and product information.

(2) Other concerns should be resolved before approval; failure to do so may render the application unapprovable.

Art. 161. - This list should also be present in the "Overview".

Non-clinical aspects

Major objections

a) Pharmacology

b) Pharmacokinetics

c) Toxicology

Other concerns

a) Pharmacology

b) Pharmacokinetics

c) Toxicology

CHAPTER VI

RECOMMENDED CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

Art. 162. - 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).

Art. 163. - More general comments could also be made here.

CHAPTER VII

REFERENCE

- Minister of Public Health Order No. 906/25.07.2006 on approval of the Analytical, pharmacotoxicological and clinical norms and protocols in respect of the testing of medicinal products;
- Minister of Public Health Order No. 895/20.07.2006 on approval of Regulations regarding marketing authorisation and supervision of medicinal products for human use;
- Notice to Applicants, Volume 2B, incorporating the Common Technical Document (CTD) May 2008. Nonclinical Overview and Nonclinical Summaries of Module 2. Organisation of Module 4;
- Questions & answers on the withdrawal of the "Note for guidance on single dose toxicity", EMA/CHMP/SWP/81714/2010;
- "Guideline on repeated dose toxicity", CPMP/SWP/1042/99 Rev. 1;
- "Duration of Chronic Toxicity Testing in Animals (Rodent and Non-Rodent Toxicity Testing)", CPMP/ICH/300/95, (ICH S4A);

- “Toxicokinetics: A Guidance for Assessing Systemic Exposure in Toxicology Studies” CPMP/ICH/384/95, (ICH S3A);
- “Guideline on the Evaluation of Control Samples in Non - clinical Safety Studies: Checking for Contamination with the Test Substance”, CPMP/SWP/1094/04;
- “Note for Guidance on Genotoxicity: Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals”, CPMP/ICH/141/95 (ICHS2A);
- “Note for Guidance on Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals”, CPMP/ICH/174/95 (ICH S2B);
- “Guideline on the Limits of Genotoxic Impurities”, CPMP/SWP/5199/02;
- Question & Answers on the CHMP Guideline on the Limits of Genotoxic Impurities, CHMP/SWP/431994/2007 Revision 3;
- “Note for Guidance on Carcinogenic Potential”, CPMP/SWP/2877/00;
- “Guideline on the Need for Carcinogenicity Studies of Pharmaceuticals”, CPMP/ICH/140/95 (ICH S1A);
- “Carcinogenicity: Testing for Carcinogenicity of Pharmaceuticals”, CPMP/ICH/299/95 (ICH S1B);
- “Dose selection for carcinogenicity studies of pharmaceuticals”, CPMP/ICH/383/95 Oct 2008 (ICH S1C Revision 2);
- “Points to Consider Document on the Non-clinical Assessment of the Carcinogenic Potential of Insulin Analogues”, CPMP/SWP/372/01;
- “Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility”, ICH Topic S 5 (R2);
- “Points to Consider on the Need for Assessment of Reproductive Toxicity of Human Insulin Analogues”, CPMP/SWP/ 2600/01;
- “Guideline on the Need for Non-Clinical Testing in Juvenile Animals on Human Pharmaceuticals for Paediatric Indications”, CHMP/SWP/169215/05;
- “Risk Assessment of Medicinal Products on Human Reproduction and Lactation: From Data to Labelling”, CHMP/203927/05;
- „Note for Guidance on Non-clinical Local Tolerance Testing of Medicinal Products”, CPMP/SWP/2145/00;
- “Guideline on the Non-Clinical Investigation of the Dependence Potential of Medicinal Products”, CHMP/SWP/94227/04;
- “Note for Guidance on Photosafety Testing”, CPMP/SWP/398/01;
- “Note for Guidance on Safety pharmacology studies for human pharmaceuticals”, CPMP/ICH/539/00 (ICH S7A);
- “Note for Guidance on the Non-clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals”, CPMP/ICH/423/02 (ICH S7B);
- “Note for Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorisation for Pharmaceuticals”, CPMP/ICH/286/95 ICH Topic M 3 (R2);

- “Note for Guidance on Non-clinical studies required before first clinical use of gene therapy medicinal products”, CHMP/GTWP/125459/2006;
- “Note for Guidance on Pre-clinical safety evaluation of biotechnology-derived pharmaceuticals” CPMP/ICH/302/95 (ICH S6);
- “Environmental Risk Assessment for Human Medicinal Products Containing or Consisting of GMO’s”;
- Guideline on the Non-Clinical Documentation for Mixed Marketing Authorisation Applications CPMP/SWP/799/95;
- “Guideline on the Non-Clinical Development of Fixed Combinations of Medicinal Products”, CHMP/SWP/258498/2005;
- “Note for guidance on non-clinical Evaluation of Anticancer Medicinal Products” CHMP/ICH/646107/08 (ICH S 9);
- “Note for guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines”, CPMP/SWP/465/95;
- “Note for Guidance on Comparability of Medicinal Products containing Biotechnology-derived Proteins as Drug Substance – Non-Clinical and Clinical Issues”, CPMP/3097/02;
- “Note for Guidance on the Investigation of Drug Interactions” Rev.1, CPMP/EWP/560/95;
- “Points to Consider on Pharmacokinetics and Pharmacodynamics in the Development of Antibacterial Medicinal Products”, CPMP/EWP/2655/99;
- “Guideline on Nonclinical Documentation for Herbal Medicinal Products in Applications for Marketing Authorisation (Bibliographical and Mixed Applications) and in Applications for Simplified Registration, Ref. CHMP/32116/2005;
- “Public Statement on the Use of Herbal Medicinal Products Containing Asarone”, CHMP/139215/2005;
- “Public Statement on the Risk Associated with the Use of Herbal Products Containing Aristolochia Species”, CHMP/138381/2005;
- “Public Statement on Capsicum/Capsaicin Containing Herbal Medicinal Products”, CHMP /138379/2005;
- “Public Statement on the Use of Herbal Medicinal Products Containing Estragole”, CHMP /137212/2005;
- “Public Statement on the Use of Herbal Medicinal Products Containing Methyleugenol”, CHMP /138363/2005;
- “Public Statement on the Allergenic Potency of Herbal Medicinal Products Containing Soya or Peanut Protein”, CHMP/138139/2005;
- “Public Statement on Chamomile Containing Herbal Medicinal Products”, CHMP/138309/2005.

Acronyms:

Log K_{ow} = octanol-water partition coefficient
PBT = persistence, bioaccumulation, toxicity
NOEC = No Observable Effect Concentration
K_{oc} = adsorption coefficient
OECD = The Organisation for Economic Co-operation and Development
CMR = carcinogenic, mutagenic, reprotoxic substances
DT50 = time in which about 50% substance is degraded
ERA = ecological risk assessment
BCF = bioconcentration factor
PEC = Predicted Environmental Concentration
CAS number = Chemical Abstract Service index number