



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Guidance document on the content of the Rapporteur's day 80 critical assessment report for generic medicinal products (Article 10.1 only)

Non-clinical and clinical aspects – generic medicinal products

<Invented Name>

<(Active Substance)>

EMA/H/C/<xxx>

Applicant:

This template/guidance is for the initial assessment of generic applications (legal basis Article 10.1) in the EU Centralised Procedure.

From a (non)clinical perspective, the primary basis for such assessment is usually the demonstration of bioequivalence. If, apart from bioequivalence studies, non-clinical data have been submitted for example to qualify impurities or to support the introduction of a new salt, a non-clinical assessment has to be performed. By analogy, additional clinical data may have been submitted (e.g. therapeutic equivalence studies) requiring a clinical assessment. In these cases the template should be supplemented with relevant headings from the respective templates of the Rapporteurs' Day 80 assessment report for full initial Marketing Authorisation Applications.



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Administrative information

< Invented > name of the generic medicinal product:	
INN (or common name) of the active substance(s):	
Active substance(s):	
Applicant:	
Applied Indication(s):	
Pharmaco-therapeutic group (ATC Code):	
Pharmaceutical form(s) and strength(s):	
Rapporteur contact person: EMA Product Lead: Procedure Manager:	Name: Tel: Fax: Email: Name: Tel: Fax: Email: Name: Tel: Fax: Email:
Names of the Rapporteur assessors (internal and external):	Non-clinical: Name(s) Tel: Fax: Email: Clinical : Name(s) Tel: Fax: Email:

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

Generic medicinal products are defined as having the same Qualitative and Quantitative composition in active substances and the same pharmaceutical form as a reference medicinal product and whose bioequivalence with the reference product has been demonstrated by appropriate bioequivalence studies.

The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regards to safety and/or efficacy. In such cases the, additional information providing proof of the safety and/or efficacy of the various salts, esters, or derivatives of an authorised active substance must be supplied by the applicant.

Also the purpose of an abridged application is to avoid the need for repetitive and unnecessary tests and trials (Recital 10 of Directive 2001/83 as amended which states that "there are reasons of public policy for not conducting repetitive tests on humans or animals without over-riding cause".

Bioequivalence studies in humans studies may not be required if the applicant can demonstrate that the generic product meets relevant criteria for exemption as defined in appropriate detailed guidelines. [See Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98]

1. Non-clinical assessment

FOR GENERIC APPLICATIONS WITHOUT NON-CLINICAL DATA

The non-clinical assessment should be performed focused on the new information. Consider the paragraph below if no new non-clinical data have been submitted.

<A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable. >

Provide the conclusion by using one of the following two options:

<Pharmacodynamic, pharmacokinetic and toxicological properties of <ACTIVE SUBSTANCE> are well known. As <ACTIVE SUBSTANCE> is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.>

<The rapporteur considers that the non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is not adequate because /.../>

If the second option is chosen, provide a detailed description of the missing information, the impact this lack of information has, and any

potential requests for additional data. This should then be translated into the draft list of questions (section 4).

In case the generic contains a different salt, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of the active substance, include the appropriate statement:

<A summary of the literature with regard to non-clinical data of {medicinal product} and justifications that the different <salt><ester><ether><isomer><mixture of isomers><complex><derivative> of the active substance does not differ significantly in properties with regards to safety and efficacy of the reference product was <not>provided and was <not>accepted by the CHMP. This is <not> in accordance with the relevant guideline and additional non clinical studies were <not> considered necessary.>

FOR GENERIC APPLICATIONS INCLUDING NON-CLINICAL DATA

New non-clinical data might exceptionally have been submitted to qualify impurities, to support the introduction of a new salt, or because new non-clinical data have become available in the framework of an update or by clinical experience, e.g. regarding pregnancy, lactation, QT, etc, which may impact the SPC. In such case a new non-clinical assessment has to be preformed. Points of interest such as recently published and clinically relevant animal data presented in the overview may be stated and commented here if necessary.

Use the relevant headings (Pharmacology, Pharmacokinetics, Toxicology) from the template of the Rapporteurs' Day 80 non-clinical assessment report for full initial Marketing Authorisation Applications to describe such information. Also the assessment may have had an impact on the SPC sections 4.6 and 5.3 (toxicology, mutagenicity, carcinogenicity, reproductive toxicity: teratogenicity, pregnancy, breastfeeding), which should be reflected hereunder.

<GLP aspects>

Statements on GLP should be addressed here and also in the "overview module" of the assessment. This section is only required for applications including new data.

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).

FOR ALL GENERIC APPLICATIONS THE SECTION "Ecotoxicity/environmental risk assessment" IS REQUIRED. Choose from one of the two options below.

1.1. Ecotoxicity/environmental risk assessment

FOR GENERIC APPLICATIONS WITHOUT ECOTOXICITY / ENVIROMENTAL DATA

<No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of <Product Name> manufactured by <Manufacturing Authorisation Holder> is considered unlikely to result in any significant increase in the combined sales volumes for all <active substance> containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.>

FOR GENERIC APPLICATIONS WITH ECOTOXICITY / ENVIROMENTAL DATA

<Summary of main study results>

Substance (INN / Invented Name):			
CAS-number (if available):			
PBT screening		Result	Conclusion
Bioaccumulation potential- log K_{ow}	OECD107 or ...		Potential PBT (Y/N)
PBT-assessment			
Parameter	Result relevant for conclusion		Conclusion
Bioaccumulation	log K_{ow}		B/not B
	BCF		B/not B
Persistence	DT50 or ready biodegradability		P/not P
Toxicity	NOEC or CMR		T/not T
PBT-statement :	The compound is not considered as PBT nor vPvB The compound is considered as vPvB The compound is considered as PBT		
Phase I			
Calculation	Value	Unit	Conclusion
PEC _{surfacewater} , default or refined (e.g. prevalence, literature)		µg/L	> 0.01 threshold (Y/N)
Other concerns (e.g. chemical class)			(Y/N)
Phase II Physical-chemical properties and fate			
Study type	Test protocol	Results	Remarks
Adsorption-Desorption	OECD 106 or ...	K_{oc} =	List all values

Ready Biodegradability Test	OECD 301				
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	DT _{50, water} = DT _{50, sediment} = DT _{50, whole system} = % shifting to sediment =			Not required if readily biodegradable
Phase I /a Effect studies					
Study type	Test protocol	Endpoint	value	Unit	Remarks
Algae, Growth Inhibition Test/ <i>Species</i>	OECD 201	NOEC		µg/L	species
<i>Daphnia</i> sp. Reproduction Test	OECD 211	NOEC		µg/L	
Fish, Early Life Stage Toxicity Test/ <i>Species</i>	OECD 210	NOEC		µg/L	species
Activated Sludge, Respiration Inhibition Test	OECD 209	EC		µg/L	
Phase I /b 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/ <i>Species</i>	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

1.2. Conclusions on non-clinical aspects

In case new non-clinical data was provided conclude on these data. Also conclude on the environmental risk assessment.

State if the SPC of the generic product is identical to the reference product. Normally it should be, but any differences should be mentioned here. State whether the differences are justified or not.

State those issues that need to be clarified. These should be carried forward to the benefit risk assessment in the Clinical part of this report, and listed in the List of Questions as appropriate.

Provide the conclusion by using one of the following two options:

<There are no objections to approval of <TRADE NAME> from a non-clinical point of view.>

OR

<As stated above, there are issues that need to be clarified, see list of questions.>

<The Rapporteur considers the following measures necessary to address the non-clinical issues:>

2. Clinical assessment

2.1. Introduction

Describe the Product profile: Indications and dosage (SPC sections 4.1 and 4.2), pharmacodynamics and pharmacokinetics of the active substance PK summary of substance and formulation; absorption, distribution, metabolism, elimination data of special interest in respect of bioequivalence studies (linearity, elimination time etc.)(see e.g. text books such as Goodman & Gilman, Martindale etc)

Relevant for the assessment <is><are> the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98) <as well as the><Guideline on Bioanalytical method validation (EMA/CHMP/EWP/192217/09)><Note for guidance on modified release oral and transdermal dosage forms: section II (pharmacokinetic and clinical evaluation) (CPMP/EWP/280/96)><Question number <NUMBER> of the Questions & Answers: Positions on specific questions addressed to the Pharmacokinetics Working Party (EMA/618604)>.

<The applicant did <not> receive CHMP Scientific Advice pertinent to the clinical investigation. <This advice concerned the following topics: [PROVIDE SUMMARY]. The applicant did <not> follow this scientific advice.>

2.1.1. GCP aspects

GCP aspects (general)

In this section specifically address:

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

GCP aspects of Human Bioequivalence studies

Bioequivalence studies are normally the sole clinical studies provided with an application for a standard generic product. Careful consideration should be given to the need for a GCP inspection of the

clinical and laboratory phases of the bioequivalence study. Particular points to consider include:

- *Has the clinical site been inspected previously by EU inspectors?*
- *Has the laboratory site been inspected previously by EU inspectors?*

This information should have been provided or will be sought by EMA.

Are there issues that may act as triggers for inspection?, e.g. :

- *Lack of inspection experience with the site*
- *Indications from the dossier that there may be problems with the analytical laboratory analysis or with the clinical conduct of the study.*
- *Location of the clinical and laboratory*

sites To request a GCP inspection:

- *Contact your local GCP inspectorate.*
- *Contact EMA inspection sector - GCP inspection coordination.*

Determine with them the clinical trial(s), sites and special concerns or issues to be addressed/the inspection. EMA inspection sector formulates the formal inspection request for review by the inspectors and agreement by the Rapporteur prior to adoption by CHMP (day 90 or 120).

2.2. Exemption

In this section describe two different kinds of biowaiver:

- *exemption for strength(s)*
- *BCS-based Biowaiver*

Refer to the respective requirements of the applicable Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98).

Also this section should be used to justify an exemption from the requirement to perform bioequivalence studies for e.g. certain dosage forms in accordance with the above-mentioned guideline.

2.3. Clinical pharmacology

2.3.1. Pharmacokinetics

To support the application, the applicant has submitted <NUMBER> bioequivalence study(ies),

<NUMBER> pharmacodynamic studies, <NUMBER > therapeutic equivalence studies.

State the reasons for submitting more than one bioequivalence trial. If there is more than one clinical study, each of them should be described separately using the below structure.

Table 1. Tabular overview of clinical studies

Study <NUMBER>: <TITLE>

Methods

Study design

Detailed description of the study design including drug intake procedures (fasting state or with food), wash-out time, meals served fed/fasted condition, constituents of meal (in fed studies), multiple/single dose, applied dose, wash-out period, blinding, crossing-over, randomization, sampling schedule, analysed compound (parent and/or metabolites) and matrix (plasma, urine data).

In case of a steady-state study, relevant details (multiple dosing).

Information about investigator, study site, protocol number, study duration, bioanalysis facility, biostatistician and/or biostatistical institute.

Critical assessment of the adequateness of the study design.

Test and reference products

Detailed information of the reference product (name) strength, pharmaceutical form, MAH, date of authorisation in EU and the detailed information (such as MA batch number and country of origin) of the batches used in the studies need to be provided in tabular format. The following information should be included: Actual strength vs. nominal strength of the test and reference products employed in the bioequivalence study, batch size of the test product employed in the bioequivalence study and commercial batch size.

Assessor's comment

The assessment should address if required data were given, if the test product is identical to the formulation intended to be marketed.

Population(s) studied

Description of number of subjects included in the study, number of subjects included in PK- and statistical analysis, drop-outs (reason why in detail), ethnicity, gender, age, health status, etcetera

Assessor's comment

The assessment should address if populations chosen is according to guidelines, inclusion/exclusion criteria ok, sample size calculation ok, ethnicity, gender, age, health status, etc. Assess potential protocol deviations/violations.

Analytical methods

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

Provide all details relevant for the assessment of the validity of the bioanalytical method in accordance with the Guideline on Bioanalytical method validation (EMA/CHMP/EWP/192217/09).

Assessor's comment

Address if the analytical method acceptable, validated, handling of samples adequate. Assess potential protocol deviations/violations.

Pharmacokinetic variables

Summarise pPharmacokinetic variables and their generation(Non-compartmental/compartmental, PK analysis software. Choice of primary and secondary variables)

Assess if Pharmacokinetic variables and methods were adequate.

Statistical methods

Description of statistical methods including prospectively defined acceptance criteria.

Assessor's comment

Assess if the statistics described were adequate, methods acceptable (transformations, parametric tests, handling of missing values, outliers, basis of bioequivalence, whether there were protocol deviations/violations and if any widening of the acceptance criteria has been adequately justified).

Results

Summarise the relevant data for the bioequivalence assessment in the below tables rather than copying detailed statistical outputs from the clinical study report.

Table X Pharmacokinetic parameters for <analyte> (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	<arithmetic> <geometric> mean	<SD> <CV %>	<arithmetic> <geometric> mean	<SD> <CV %>
<AUC _(0-t) > <AUC _(0-72h) >				
AUC _(0-∞)				
C _{max}				
T _{max} *				
<AUC _{0-t} >	area under the plasma concentration-time curve from time zero to t hours>			
<AUC _{0-72h} >	area under the plasma concentration-time curve from time zero to 72 hours>			
AUC _{0-∞}	area under the plasma concentration-time curve from time zero to infinity			
C _{max}	maximum plasma concentration			
T _{max}	time for maximum concentration (* median, range)			

Table X Statistical analysis for <analyte> (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV % *
<AUC _(0-t) > <AUC _(0-72h) > C _{max}			
* estimated from the Residual Mean Squares			

In case steady state studies have been performed, similar tables should be produced reporting the parameters AUC_{0-t}, C_{max}, C_{min}, and fluctuation index (PTF%).

Safety data

Provide a very brief summary of the adverse events observed in the bioequivalence study. No conclusion in terms of comparison between test and reference should be made based on these data.

Conclusions

<Based on the presented bioequivalence study(ies) <(INVENTED) NAME> is considered bioequivalent with <REFERENCE PRODUCT>.

OR

<Due to the following reasons < ELABORATE ON THE REASONS > <(INVENTED) NAME> is not considered bioequivalent with <REFERENCE PRODUCT>.

If applicable; The results of study <STUDY NUMBER> with <XXmg> formulation <CAN/CAN NOT> be extrapolated to other strengths <XX mg>, according to conditions in the relevant Guidelines.

2.3.2. Pharmacodynamics

<No new pharmacodynamic studies were presented and no such studies are required for this application.>

If applicable, usually no new data required and given. Required, if bioequivalence cannot be shown by pharmacokinetic studies in order to substantiate therapeutic equivalence.

Assessor's comment

2.3.3. Post marketing experience

Consider any evaluation of the safety data submitted (if the product has already been on the market elsewhere outside EU). However this is rarely available; Note that this information relates to the medicinal product and not the active substance.)

The following case is more likely:

<No post-marketing data are available. The medicinal product has not been marketed in any country.>

2.3.4. Discussion on clinical aspects

Discuss critical design elements particularly if different from the standard cross-over design, e.g. parallel design, fed versus fasting state, investigation in patients, etc. Any relevant of the analyte (parent versus metabolite) as well as the bioanalytical method should be discussed. Also reflect on the pre-specified acceptance criteria for bioequivalence, particularly if scaling is applied for highly variable drugs (e.g. has a replicate design been employed to estimate the CV?) or for narrow therapeutic index drugs.

For the results, state whether the pre-set bioequivalence criteria were met. Also summarise any issues with regard to the conduct of the study (e.g. withdrawals/replacement of subjects). In case of conduct of more than study against the EU reference product, assess the conclusiveness of the available data.

Any concerns with regard to the GCP compliance of the study should be clearly described and discussed.

In case efficacy issues have been identified for inclusion in Annex II as conditions, it needs to be motivated in the CHMP AR, notably it

should be explained in the context of a positive benefit/risk balance and, taking into account the situations listed in the Commission Delegated Regulation (EC) No 357/2014. The justification should provide explicit information as to which situation(s) it corresponds.

2.3.5. Conclusions on clinical aspects

Conclude on clinical aspects and carry forward open issues to the list of questions.

In case the generic contains a different salt, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of the active substance, include the appropriate statement:

<A summary of the literature with regard to clinical data of { medicinal product} and justifications that the different <salt><ester><ether><isomer><mixture of isomers><complex><derivative> of the active substance does not differ significantly in properties with regards to safety and efficacy of the reference product was <not>provided and was <not>accepted by the CHMP. This is <not> in accordance with the relevant guideline and additional clinical studies were <not> considered necessary.>

Whenever there is an impact on the Benefit / Risk, please elaborate here on the clinical issue (s) that led to this conclusion:

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

<The Rapporteur considers the following measures necessary to address the clinical issues:>

3. Pharmacovigilance

3.1. Risk management plan

<Safety Specification>

If any data on Safety Specifications Parts II SI to SVII are submitted by the applicant, the rapporteur can complete this section.

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

Summary of the safety concerns

Copy and paste the summary of safety concerns (table 3) from Part II Module SVIII; for older-style RMPs copy the summary on safety concerns from section 1.10.

The Applicant identifies the following safety concerns

Table X: Summary of safety concerns

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

Assessor's comment:

Comment on whether the applicant's proposal is adequate based on the assessment of the provided data and in line with the reference product.

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

Having considered the data in the safety specification,

- <The Rapporteur agrees that the safety concerns listed by the Applicant are appropriate.>

or

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

<In line with the reference product, the Rapporteur considers that the following should also be <a> safety concern(s):>

<In line with the reference product, the Rapporteur considers that the following should not be <a> safety concern(s):>

The issues to be addressed must be included in the List of Questions.

3.2. Pharmacovigilance system

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

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

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

Assessor's comment

4. List of questions as proposed by the Rapporteur

Non-clinical aspects

Major objections

<None.>

<Pharmacology>

<Pharmacokinetics>

<Toxicology>

Other concerns

<None.>

<Pharmacology>

<Pharmacokinetics>

<Toxicology>

Clinical aspects

Major objections

<None.>

<Pharmacokinetics>

<Risk management plan>

<Pharmacovigilance system>

Other concerns

<None.>

<Pharmacokinetics>

<Risk management plan>

<Pharmacovigilance system>

5. List of references