3. Notification

on the clinical trial of medicinal products for human use.

A joint publication of the Federal Institute for Drugs and Medical Devices and the Paul Ehrlich Institute

for the request to the competent authority for the authorisation of a clinical trial according to § 40 para. 1 sentence 2 of the German Medicines Act (*Arzneimittelgesetz,* AMG), as well as § 7 of the statutory regulation according to § 42 para. 3 of the AMG (GCP-V) for the notification of subsequent amendments during the conduct of the clinical trials according to § 10, as well as for the notification of the end of the clinical trial according to § 13 paragraph 8 and 9 of this statutory regulation.

August 10, 2006

Table of contents

Index of appendices

Appendices to section V

Appendix V / 1

Schematic overview of the statements on the properties of the testing preparation(s) in accordance with the recommendations of *Guideline CPMP/ICH/291/95*, which, as a rule, are expected before the commencement of clinical trials in phases I, II, III, and IV

Appendix V / 2

Clinical documents for the authorisation request.

Explanations on the guidelines in Addendum 4 "*Common technical document headings for clinical data*" of "*Detailed guidance for request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial*"
(Guideline ENTR/CT 1)

I. Introduction

This notification describes in form and content the requirements for the documentation to be submitted with the request for the authorisation by the competent authority of a clinical trial of medicinal products for human use according to **§ 42 para. 2 German Medicines Act (AMG)**, as well as **§ 7 para. 1, 2, 4, 5, 6 and 7 of the GCP-V**, as well as the requirements according to **§ 10 para. 1 and 3** (subsequent amendments) and according to **§ 13 para. 8** (notification of the end of the clinical trial) and **9** (summary of the final report) of the GCP-V. **Directive 2001/20/EG** and its implementation in national law serve to harmonise the regulatory requirements for clinical trials of medicinal products for human use in the European Union member states. The rights, safety and well-being of all participants in clinical trials should thus be ensured. The observance of internationally recognised quality requirements for the planning, conduct and documentation of clinical trials should guarantee the credibility of the results. Bureaucratic hindrances between the member states should be overcome, and the conduct of clinical trials should be accelerated, especially in event of multinational or multicentric trials.
Short processing periods in the authorisation process help enable clinical trials to commence without delay. This can only be put into practice when the requests for authorisation are structured as uniformly as possible and the statements and documents for the investigational medicinal products are presented in such a way that the benefit and risk of their use can be evaluated. This notification should help the applicant to prepare an authorisation request and explain legal requirement of the AMG and the GCP-V.
The provisions of the AMG on the clinical trial of medicinal products for humans apply to all investigational medicinal products and include the following groups of medicinal products:

a) pharmaceuticals with chemically-defined active substances;

b) biotechnologically produced pharmaceuticals;

c) somatic or xenogenic cell therapeutics;

d) pharmaceuticals for gene therapy;

e) immunological pharmaceuticals such as vaccines, allergens, immune sera;

f) blood preparations;

g) herbal medicinal products;

h) radiopharmaceutical products;

i) homeopathic and anthroposophic pharmaceuticals

The extent of the documents to be submitted for the authorisation of a clinical trial depends on the type of investigational medicinal products, the status of their development and their conditions of implementation in the clinical trial applied for.
The requirements are generally based on the guidelines from the *Note for guidance on general considerations for clinical trials (CPMP/ICH291/95)* and the relevant guidelines[1] on special queries. Deviations from these recommendations may be necessary in specific cases for medical, methodical or ethical reasons; although these are to be explained and substantiated.

[1] http://ec.europa.eu/enterprise/pharmaceuticals/index_en.htm

An evaluation according to **§ 42 para. 2 AMG** is to be conducted on the basis of these documents, particularly of the safety of the affected persons[2] in comparison with the intended study population, the criteria for inclusion and exclusion, the concomitant medications to be expected or excluded, as well as planned supervision measures.

II. Index of the documentation to be submitted by the sponsor with the request for authorisation

The following documents and information are to be submitted with the request for authorisation to the competent authority in electronic and written form:

1. An accompanying letter in German signed by the sponsor[3] or his representative or proxy with the corresponding power of attorney in German or English specifying

   a) the name or company and the address of the sponsor and, if present, his representative located in the European Union or other contracting state of the Treaty on the European Economic Area,

   b) the EudraCT number of the clinical trial,

   c) the trial protocol code of the sponsor,

   d) the title of the clinical trial,

   e) indications of particularities of the clinical trial and references to the sources of the applicable information in the documents presented (for example first-time administration of the active substance to humans, administration to a special population of test subjects or patients, etc.),

   f) a confirmation that the documents submitted in paper form are identical to those submitted in electronic form;

2. the completed application form in written and electronic form[4];

3. the copy of the confirmation for the EudraCT number assigned by the European Databank;

4. the trial protocol[5] signed by the sponsor or his representative and, in the event of mono-centric trials, signed by the principal investigator or investigator, or, in the event of multicentric trials with multiple trial sites, signed by the coordinating investigator, specifying the EudraCT number, complete title and, if applicable, the short title of the clinical trial, the sponsor's trial protocol code, the version and date of authorisation on the cover page;

5. a plan for the further treatment and medical supervision of the affected persons after the end of the clinical trial according to **§ 7 para. 2 no. 13 GCP-V**;

6. justification corresponding to the trial goal for the gender distribution of the group of affected persons according to **§ 7 para. 2 no. 12 GCP-V;**

[2] Definition according to **§ 3 para. 2a GCP-V**
[3] according to **§ 4 para. 24 AMG**
[4] Annex 1 of the ENTR/CT 1 guideline
[5] Trial protocol according to **Note for guidance on good clinical practice, No. 6: Clinical trial protocol and protocol amendments (CPMP/ICH/135/95)**

7. confirmation according to **§ 7 para. 2 no. 15 of the GCP-V** that the persons affected shall be informed of the dissemination of their pseudonymous data in the scope of the documentation and notification obligations according to **§ 12** and **§ 13 GCP-V** to the recipient named therein, with the explanation that affected persons not consenting to the dissemination of information cannot be included in the clinical trial;

8. names and addresses of the facilities which, as trial sites or trial laboratories, are involved in the clinical trial, as well as those of the principal investigators and the coordinating investigator of the clinical trial.
(Explanatory note added to this translation: the principal investigator is the responsible investigator for one trial site where several subinvestigators may be involved, the coordinating investigator[6] is responsible for the clinical trial.

9. The investigator's brochure in accordance with the *Note for Guidance on Good Clinical Practice, CPMP/ICH/135/95, Nr. 7: Investigator's Brochure (IB)* specifying the version and date of authorisation on the cover page;

10. statement of the professions of those investigators who are not physicians, the scientific requirements of their respective professions and experience in patient care prerequisite of the pursuit of his profession, as well as demonstration that the respective profession is qualified to carry out research on humans, and demonstration of the particular circumstances of the clinical trial justifying the member of the respective profession to act as an investigator according to **§ 7 para. 2 Nr. 6 of the GCP-V**;

11. the Investigational Medicinal Product Dossier (IMPD) with the following content:

    a) documents on quality and manufacturing;

    b) documents on pharmacological / toxicological trials;

    c) draft of the intended designation of the investigational medicinal product corresponding to **§ 5 GCP-V**;

    d) the manufacturing license of all manufacturers with headquarters in the EU or the European Economic Area in copy;

    e) if applicable, the license for importation to the EU in copy;

        - for importers with headquarters in Germany according to **§ 72 AMG,**

        - for importers with headquarters in another member state of the EU according to Article 13 para. 1 of the **Directive 2001/20/EG**

    in addition to the importation license, a GMP compliance certificate signed by the competent representative of the importer is to be submitted

    f) documents on the results of hitherto conducted clinical trials, as well as further published clinical findings

    g) summary of the benefit-risk assessment

[6] German: Leiter der klinischen Prüfung

For the standardisation of the IMPD at the EU level, the documents can be submitted to the IMPD separately according to **GCP-V § 7 para. 4 no. 1 letters c), d), and e)**. If the statements required according to **§ 7 para. 4 no. 1 letters b), f) and g)** GCP-V are already documented in the Investigator's Brochure, the corresponding sections of this document may be referenced in the IMPD. Required supplements resulting from the current level of knowledge are to be specified to the IMPD in an addendum. A record of the amendments carried out is to be attached with the submission of an amended version of the IMPD. If the investigational medicinal product is a placebo, the content of the IMPD is limited to the documents on quality and manufacture according to **§ 7 para. 4 no. 1 letters a) and c) of the GCP-V**.

The investigator's information is to be validated and updated by the sponsor at least once per year. Renewed submission is only necessary in the event of substantial amendments according to **§ 10 para. 1 of the GCP-V** (see below, **section VII**).

Investigational medicinal products containing active substances that are generally known and are used in connection with a clinical trial to produce specific reactions (**§ 3 para. 3 of the GCP-V**), and are employed under the conditions stated in **Annex 13 Revision 1 Note**[7] do not require a complete IMPD, as long as the substances they contain are not of biological origin. By means of the material on scientific findings submitted, the sponsor should substantiate that the application of the substance in the scope of the production of specific reactions is known and, with respect to the planned application in the clinical trial, harmless. In this case, only the certification of release by a competent person[8] is to be submitted.

For investigational medicinal products already approved in a member state of the European Community, the Summary of Product Characteristics (SmPC, see **Appendix II / 1**) may be submitted in place of the dossier in accordance with the conditions specified in **§ 7 para. 5 of the GCP-V**. In this case, the submission of the investigator's information is also omitted according to
No. 9;

12. proof of insurance according to **§ 42 para. 2 no. 3 AMG** in connection with **§ 40 para. 1 sentence 3 no. 8 and para. 3 AMG**, if the investigational medicinal product is a xenogenic cell therapeutic;

13. the documents according to **§ 7 para. 4 no. 3 of the GCP-V** for investigational medicinal products containing genetically modified organisms[9];

14. the name and address of the competent ethics committee according to **§ 42 para. 1 sentence 1 and 2 of the AMG** and the name and address of the competent authorities of the other European Union member states and other contracting states of the Treaty on the European Economic Area in which the clinical trial is to be implemented:

15. if applicable, substantiated statements of negative evaluations of the competent ethics committees of other European Union member states or other contracting states of the

[7] **Annex 13 Revision 1, July 2003 (F2/BL D2003): Page 1, note**
[8] see Article 13 para. 2 of the Directive **2001/20/EG**
[9] For investigational medicinal products consisting of or containing a genetically modified organism or combination of genetically modified organisms, an exposition and assessment of the health risks to the environment and persons not concerned, as well as an exposition of the precautions scheduled, and, according to Addendum III of this directive, further information which is specified there in greater detail, are to be submitted to the competent authority according to § 7 (4) 3 of the GCP of August 9, 2004 according to Addendum II of Directive 2001/18/EG of the European Parliament and European Council on the intentional release of genetically modified organisms in the environment.

Treaty on the European Economic Area, as well as requests for authorisation rejected by competent authorities of other European Union member states or other contracting states of the Treaty on the European Economic Area are to be specified, provided that they pertain to the investigator's information, the IMPD or an authorisation by the competent authority provided under stipulations;

16. if a shortened term of authorisation according to **§ 9 para. 3 of the GCP-V** is intended to be applied for, it should be specified on the cover letter and confirmed that the statements of the request already authorised remain unchanged according to **§ 7 para. 4 no. 1 a) and b) of the GCP-V**;

17. indication of whether the matter concerns a subsequent study of a trial in phase I-III already authorised by the German competent authority for the purposes of numbers **18. 1.2 – 18.1.7.2** of the AMG Cost Ordinance (***AMGKostV***); where this applies (irrespective of the trial protocol), then the submission number of the German competent authority as well as amendments to the documentation such as IMPD or investigator's brochure in comparison to the previously submitted trial should be stated briefly.

If the investigational medicinal product is the subject of a clinical trial already authorised to the sponsor by the German competent authority, then the sponsor may refer to the documents submitted in the scope of the previous authorisation procedure for the investigational medicinal product. Furthermore, it is possible to refer to data of another applicant if an authorisation letter is submitted for this purpose. Additionally, in well-founded individual cases, an adapted, adequate content of the IMPD can be agreed upon with the German competent authority before the filing of the application. If further findings on the quality and manufacturing, pharmacological-toxicological trials or clinical findings which are not part of the documents on the investigational medicinal product are available to the sponsor, they are to be submitted.

If a scientific consultation with the competent authorities of the member states or a *scientific advice* at the EMEA have been conducted, it is requested that the protocols of these deliberations be attached to the request for authorisation.

All documents are to be submitted in written form in quadruplicate. The letter named in no. 1 is to be submitted in German; the documents under nos. 3 to 17 may be submitted in either English or German. Since the competent higher federal authority is obligated to transfer the data to be submitted in the application form to the EudraCT databank, we request that the electronic version of the application form available at the **EudraCT internet site of the EMEA**[10] in English be used, that all statements be made in English and that four hard copies of the completed form, as well as in electronic form on a CD-ROM as XML and PDF files, be submitted. In doing so, it should be ensured that the statements in both files are identical. We request that the documents designated under no. 1 and nos. 3 to 17 be submitted on the same CD-ROM as the PDF files and saved in the given numerical order. Further requirements for the submission of the documents in electronic form are regulated in a separate explanation on the execution of the GCP-V[11].

Additional documents to be submitted to the Federal Opium Agency for clinical trials with narcotics

1. From the sponsor:

[10] **http://eudract.emea.eu.int/**

[11] Currently still in progress, publication shall take place on the internet sites of the BfArM (*Bundesinstitut für Arzneimittel und Medizinprodukte*) and PEI (*Paul-Ehrlich-Institut*)

Copies of both the cover letter mentioned above under **1.** and the trial protocol listed under **4.**

2. From the investigator (in accordance with § 7 BtMG [*Betäubungsmittelgesetz*-German Narcotics Act])

a) the investigator's full name (all given names, surname and birth name, if applicable) and personal information (date and place of birth, home address, citizenship),

b) as proof of the technical knowledge required according to **§ 6 para. 1 no. 3 BtMG**, a copy of the licence to practice medicine or a copy of a university degree qualifying the holder to act as investigator in his practiced profession. If the investigator has already received a narcotics number from the Federal Opium Agency, the statement of this number shall suffice,

c) type and amount of the narcotic to be implemented by the investigator in the scope of the clinical trial, including specification of the supplier,

d) the exact designation and address of the facility in which the clinical trial is to be conducted, specifying telephone number and, if applicable, fax number,

e) description of the safety measures present against the unauthorised removal of narcotics, specifying type of safes and accommodations provided for the storage of narcotics,

f) dated signature of the physician,

The implementation of narcotics in clinical trials is subject to **§ 3 BtMG**. Each investigator is only allowed to begin with the clinical trial upon receiving permission from the Federal Institute for Drugs and Medicinal Products (*BfArM*) according to **§ 3 BtMG**.

3. From the narcotic supplier

The establishment supplying the narcotics to the investigator is also to submit an application according to **§ 7 BtMG**.

III. Chemical/pharmaceutical and biological documentation requirements for investigational medicinal products for phases I - III

According **§ 42 para. 2 sentence 2 AMG**, the sponsor is to submit for evaluation, among others, summarised statements on the analytical trial of the pharmaceutical required for the evaluation to the German competent authority. In accordance with guideline **ENTR/CT 1**, these statements should be presented in Common Technical Document (CTD) structure (**Notice to applicants, Volume 2B, Medicinal products for human use, Presentation and content of the dossier**). **Appendix III / 1** to Section III describes the general requirements for the chemical/pharmaceutical and biological documentation to be submitted with the request for authorisation of investigational medicinal products for clinical trials of phases I-III. Deviations from the requirements described are to be justified.
The extent of the informational material submitted in the scope of clinical trials of phases II and III should reflect the progress of the investigational medicinal product. Exemplary requirements for the chemical/pharmaceutical and biological documentation for clinical investigational medicinal products in generic bioequivalence studies as well as for authorised, unmodified and modified reference medicinal products are described in **Appendices III / 2-4** to Section III.

The requirements described in this notification refer to the documents to be submitted in the scope of the authorisation procedure. Additional requirements for the manufacture of investigational medicinal products in accordance with the GMP (Good Manufacturing Practice) remain unaffected. Attention is called especially to the obligation to follow the Operation Ordinance for Pharmaceutical Entrepreneurs (*Betriebsverordnung für pharmazeutische Unternehmer*) in the respective applicable version, with which the requirements for investigational medicinal products in **Directive 2003/94/EC** have been implemented in national law.

IV. Preclinical documentation requirements for investigational medicinal products

1. Introduction

The extent of the preclinical research required for the authorisation of clinical studies is described in general form in the **Note for guidance for non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals (CPMP/ICH/286/95)**. Statements on the preclinical documentation are to be submitted in such a manner that the pharmacological/toxicological properties of the investigational medicinal product may be evaluated and that the risks of the application of the investigational medicinal product inferable from them may be assessed. The guidelines on preclinical studies released by the European Community are to be followed for certain investigational medicinal products such as cytostatic drugs, biotechnologically manufactured investigational medicinal products, vaccines and blood preparations.
For certain investigational medicinal products such as vaccines, blood preparations, therapeutic allergens and biotechnologically manufactured pharmaceuticals, certain studies, for example on mutagenicity, carcinogenicity as well as reproduction toxicity are not required or required only on a restricted basis. Specifically for the implementation of clinical trials with the singular administration of so-called micro doses (up to 1/100 of the calculated dosage at which the investigational medicinal product shows a pharmacological effect), the required research in the **Position paper on non-clinical safety studies to support clinical trials with a single microdose (CPMP/SWP/2599/02)** may be sufficient. A product-specific, reduced preclinical documentation is acceptable for “biosimilar products” according to Article 10(1)(a)(iii) of **Directive 2001/83/EC** and part II of Addendum I of **Directive 2001/83/EC**, in the respective valid version of each.

1.1 Implementation of preclinical studies

The preclinical studies on safety pharmacology and toxicology required in the **Note for guidance for non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals (CPMP/ICH/286/95)** are to be conducted in accordance with the regulations on Good Laboratory Practice (GLP). The sponsor is to justify deviations from the guidelines and submit a statement on the GLP status of the studies (see **ENTR/CT 1** Section 4.1.6.1.2). If the toxicity studies are supplemented with toxicokinetic investigations, these are to be conducted in accordance with the **Note for guidance on toxicokinetics – The assessment of systemic exposure in toxicity studies (CPMP/ICH/384/95)**.

1.2 General principles on preclinical documentation

The documentation should be structured according to Appendix 3 of guideline **ENTR/CT 1**. It should contain an overview of all relevant preclinical studies, as well as all relevant data on methods, findings (preferably in tabular form), and the discussion thereof. Complete study data and copies of the references cited should be provided upon request (see **ENTR/CT 1** Section 4.1.6.1.2).

If the statements on the preclinical studies are submitted in the scope of an independent IMPD, the documentation should be structured according to the 'Tabulated formats and summaries' of the CTD. For known substances, the suitability of submitted documents not specific to medicinal substances is to be substantiated[12].

1.2.1 Short summary of the preclinical studies

The summary of the preclinical study findings may be in tabular form and should essentially contain a characterisation of the test system (cell type or line, species, phylum, gender), treatment (investigational medicinal products, type of application, dose or concentration, duration of exposure), the GLP status, study code and relevant findings. In principle, the report should be oriented to Section 7.3.5 of Good Clinical Practice presented in **CPMP/ICH/135/95**.

1.2.2 Discussion and conclusion

The entirety of the findings of all relevant preclinical studies should be discussed and evaluated with regard to the safety of the investigational medicinal product. The following points should be particularly taken into consideration:

a) Relevance of the animal models and species differences including the findings from research on human cells/tissues;

b) Dose dependency of the observed effects including differentiation between No Observed Effect Level (NOEL) and No Observed Adverse Effect Level (NOAEL);

c) the complete or partial reversibility of the changes induced, in cases of discontinuation trials;

d) safety margins, preferably referring to exposure, regarding effects relevant to safety in preclinical studies and in the intended application with humans;

e) additional supervision parameters relevant to safety in the clinical studies to be deduced from the findings;

f) interactions with other active substances, to the extent known;

g) potential differences between the batches of the investigational medicinal product implemented in the preclinical investigation and those intended for the clinical trial, to the extent that data is present. Data is to be submitted in cases of changes to the extract specification of herbal pharmaceuticals between preclinical and clinical trials producing the reference to the composition of the extract implemented in the preclinical trials.

h) for gene transfer pharmaceuticals, the investigations should reflect the vector as well as the gene products.

2. Documentation of the preclinical trials

See **Appendices IV / 1 – 4** to Section IV.

V. Requirements for the clinical documentation

[12] Directive 2003/63/EC of the 25. June 2003 amending Directive 2001/83/EG of the European Parliament and of the Council on the Community code relating to medicinal products for human use.

1. General instructions

The sponsor is to submit all clinical statements and documents on the investigational medicinal product which are necessary for the evaluation of the application to the German competent authority with the request for authorisation according to **§ 42 para. 2 sentence 2 AMG**. According to guideline **ENTR/CT 1** Section 4.1.6.1.3, this concerns the summaries of all relevant data from the clinical trials conducted by the sponsor up to the time of the application's filing, as well as results from previously conducted on humans, if applicable. Both favourable as well as unfavourable findings are to be represented in these summaries and are, as far as required, to be supplemented by relevant statements from other scientific sources. If the statements on the human pharmacological and clinical trials are submitted in the scope of an independent IMPD, it is recommended to structure the documentation according to the 'Tabulated formats and summaries' of the CTD. If the Investigator's Brochure (IB) is referenced, it is recommended to structure the documentation according to Addendum 4 of guideline **ENTR/CT 1** (see **Appendix V / 2** to Section V for further explanation on this). For known substances, the suitability of submitted documents not specific to medicinal substances is to be substantiated[13].
GCP conformity is to be substantiated for statements and documents from previously conducted and concluded trials included in the report. If this cannot be carried out at the time of the application's filing, the reasons for this as well as a brief estimation of the credibility of the findings contained in the documents are to be presented. This can be carried out in the form of a GCP declaration as Addendum to the IMPD.

1.1 Requirements for the clinical documentation dependent on the phases of the clinical trials

Table 5 in Appendix V / 1 gives an overview of the statements on the properties of the investigational medicinal product(s) before the commencement of clinical trials in phases I, II, III and IV which as a rule are expected according to the recommendations of Guideline **CPMP/ICH/291/95**. If this information is not present in the Investigator's Brochure, it is to be submitted separately in the IMPD. The instructions in **Appendix V / 2** provide suggestions on the layout of the clinical documentation content and do not present any requirements exceeding those of guideline **ENTR/CT 1**. If the use of a medicinal product authorised in the EU as an investigational medicinal product outside of the conditions of authorisation (indication, dose range, duration of treatment, pharmaceutical form or type of application) is intended, the SmPC submitted as a simplified IMPD is to be supplemented, where applicable, by summarised reports on the findings of previously conducted clinical trials or other clinical data on the effects and risks.

1.1.1 Clinical trials in phases I and IIa

If authorisation is applied for in phases I and IIa, a listing of all clinical trials with the same active substance completed by the sponsor[14] in phases I and IIa is to be submitted, specifying the range of doses investigated, the number of people per dosage group and the duration of treatment and, if applicable, statements on the gender distribution. Furthermore, a list of suspected unexpected serious adverse reactions (SUSAR) is to be submitted, which should be classified, if possible, according to dosage, application duration of the investigational medicinal product and degree of severity as well as chronological sequence and, if applicable, gender-specific differences. For studies in phases I and IIa in which the same active substance has already been tested in other contexts in clinical trials in phases IIb and III, it shall suffice to submit the Investigator's Brochure, as well as a list of all cases of SUSARs classified according to the dosage and application duration of the investigational medicinal product as well as according to degree of severity and chronological sequence, if this has not yet been included in the Investigator's Brochure. If the

[13] See Directive 2003/63/EC
[14] End of study in accordance with the determination in the trial protocol. As a rule according to Para. 4.3.2.1 of guideline **ENTR/CT 1**.

investigation of pharmaceuticals authorised in the EU as investigational medicinal products outside of the conditions of authorisation (indication, dose range, duration of treatment, pharmaceutical form or type of application) in phases I and IIa of the clinical trials is intended, the SmPC submitted as a simplified IMPD is to be supplemented where applicable by summarising reports on the findings of previously conducted clinical trials or other clinical data on the effects and risks.

If available at the time of the application's filing and not already presented in the Investigator's Brochure, statements should be included on the state of knowledge of the pharmacodynamic effects on humans hitherto investigated regarding type and dose dependency as well as on the pharmacokinetics of the active substance(s) and, if applicable, the active metabolites. For vaccines, statements on immune reaction in humans should be submitted.

1.1.2 Clinical trials in phases IIb and III

If authorisation is applied for in phases IIb and III, a listing is also to be submitted of all clinical trials in phases I-III with the same active substance already concluded by the sponsor specifying the dose range investigated, number of people in each dosage group, duration of treatment, and, if applicable, gender distribution. In addition to the Investigator's Brochure, a list of all suspicious cases of SUSARs is to be submitted, which is to be classified according to dosage, duration of application of the investigational medicinal product and degree of severity as well as chronological sequence, if these are not already included in the Investigator's Brochure. In addition, statements from explorative or confirmatory dose-finding studies of phase II on the state of knowledge on the efficacy and safety of the investigational medicinal product in the intended dose range are to be submitted before phase III. Proven dose-effect relations and, if applicable, dose-toxicity relations should be described on the basis of the investigated parameters on the efficacy as well as tolerance. If medicinal products authorised in the EU are intended to be used as investigational medicinal products outside of the conditions of authorisation (indication, dose range, duration of treatment, pharmaceutical form or type of application) in clinical trials of phases IIb and III, the SmPC submitted as simplified IMPD is to be supplemented, where applicable, by summarising reports on the findings of previously conducted clinical trials or other clinical data on safety and efficacy.

1.1.3 Clinical trials of phase IV

As long as the conditions of phase IV are fulfilled, the submission of the SmPC shall suffice. Further information can be obtained in **Table 2 in Appendix II / 1**.

1.2 General principles for the documentation of clinical-pharmacological as well as clinical trials

With every application for authorisation, informative and summary statements on previously conducted clinical trials should be submitted, from which the application conditions of the investigational medicinal product in the clinical trial currently being applied for, as well as its objective and design can be deduced. If the Investigator's Brochure contains the required statements, the respective sections can be referenced (confer: Appendix 4 of the guideline **ENTR/CT 1**). Data resulting from other relevant studies should additionally be graphically represented, to the extent that this is possible and meaningful. The presentation should contain statements for each clinical trial on the following points:

a) EudraCT number (if applicable),

b) the sponsor's code for the clinical trial,

c) short title of the clinical trial,

d) type of clinical trial,

e) affected persons (number, if applicable, number of women and men, inclusion of particular groups of people)

f) methods for the ascertainment of objective parameters,

g) type of application / pharmaceutical form and duration of application,

h) dosage of the investigational medicinal products,

i) comparison groups including placebo group,

j) relevant positive and negative results,

k) statistics, if applicable.

Other relevant information on the investigational medicinal product obtained in humans outside of clinical trials is to be presented correspondingly in these documents.

VI. Summary of benefit-risk assessment

According to guideline **ENTR/CT 1** Section 4.1.6.1.4, all data reported from preclinical and clinical investigations regarding the expected benefits and potential risk for the affected persons should be critically analysed and evaluated in an integrated summary. The summary of the benefit-risk evaluation should be carried out with regards to the pharmacodynamic / immunological spectrum of effects as well as the clinical efficacy and safety of the affected persons in consideration of the following aspects, among others:

a) the intended exposure of the affected persons to the clinical medicinal product to be tested and its metabolites (dosage or plasma concentrations) in relation to the exposures at which relevant effects in the preclinical and clinical investigations on pharmodynamics, toxicology as well as efficacy and tolerance have been ascertained (including the statement on safety factors, if expedient);

b) dose-effect relationships and dose-toxicity relationships, as well as optimal dose ranges including justification for the dosages intended in the clinical trial applied for;

c) efficacy and safety in particular populations (for example gender, age, children, organ function, illnesses, genetic polymorphisms);

d) findings from investigations on interactions with other active substances regarding the study population intended in the clinical trial applied for or concomitant medication anticipated;

e) necessary supervision of the parameters on the basis of the state of knowledge on possible risks for the persons affected;

f) intended measures and criteria for prematurely aborting or interrupting the clinical trial, should it become necessary.

Additional or other trial parameters for benefit-risk assessment are to be taken in consideration to some extent for biologically or biotechnologically manufactured pharmaceuticals, for example virus safety, persistence of the protection, duration of the gene expression, absence of germline gene transfer. If the benefit-risk assessment is present in the trial protocol, it can be referenced.

VII. Subsequent amendments

Amendments to the documents submitted with the request for authorisation are only possible upon receipt of a list of faults in accordance with **§ 9 para. 1 GCP-V** (application not in proper form) or upon notification of objections substantiated by reasons by the higher federal authority according to **§ 9 para. 2 GCP-V**. Amendments or supplements after the issuance of authorisation are according to **§ 10 para. 1 GCP-V** subject to authorisation by the German competent authority, if they are capable of:

a) having an effect on the safety of the persons affected,

b) influencing the interpretation of the scientific documents supporting the trial, or the scientific significance of the study findings

c) considerably altering the type of leadership or implementation of the study,

d) affecting the quality or safety of the investigational medicinal product or

e) altering the assessment of risk to the health of non-affected persons or the environment in cases of clinical trials with pharmaceuticals consisting of or containing genetically modified organisms.

Amendments that are only subject to authorisation on the part of the competent ethics committee are also to be reported to the German competent authority. The form in Annex 2 of guideline **ENTR/CT 1** is to be used for the authorisation request of a subsequent amendment. The following statements and documents are to be submitted in electronic and written form with the authorisation request for an amendment subject to authorisation:

1. An accompanying letter signed by the sponsor, his representative or authorised agent in German with the suitable power of attorney[15] in German or English specifying:

   a) the name or company and address of the sponsor and, if present, of his representative residing in the European Union or other contracting country of the Treaty on the European Economic Area,

   b) the submission number of the German competent authority

   c) the EudraCT number of the clinical trial

   d) the sponsor's trial protocol code

   e) the title of the clinical trial

   f) whether the amendments pertain to
      - the pharmaceutical quality
      - the findings of the preclinical trials
      - the findings of the clinical trials and/or other amendments

2. The completed application form in accordance with Annex 2 of guideline **ENTR/CT 1**.

[15] The power of attorney can be omitted if the authorised agent is same as the one who initially filed the application for authorisation.

3. If the amendments according to **§ 10 para. 1 GCP-V** affect contents of the application form submitted upon the initial filing of the application for authorisation of this clinical trial according to **ENTR/CT 1**, an updated XML file with a corresponding PDF file is also to be submitted.
4. Furthermore, the documents specified under II no. 5 and nos. 8-15 of the initial application are to be submitted, insofar as they are affected by the amendments which are subject to authorisation.

The following examples of amendments may be required during a clinical trial, yet not all of these amendments – depending on the individual case – need necessarily be classified as subject to authorisation. The sponsor is to verify whether an amendment is to be classified as subject to authorisation according to **§ 10 GCP-V**. Irrespective of **§ 10 GCP-V**, the sponsor and investigator are, according to **§ 11 GCP-V**, to take all necessary measures in the protection of the affected persons from immediate danger without delay, if new circumstances might compromise the safety of the affected persons.

1. Subsequent amendments to statements on pharmaceutical quality

Amendments to data on quality of the investigational medicinal product in the IMPD:

a) importation of the investigational medicinal product,

b) name or code of the investigational medicinal product,

c) primary means of packaging,

d) manufacturer of the active substance,

e) manufacturing/synthesis procedure of the active substance,

f) specifications of the active substance,

g) manufacturing procedure of the investigational medicinal product,

h) specifications on the release or lifespan of the investigational medicinal product,

i) specifications of ancillary substances which could influence the performance of the product,

j) period of usability including stability after opening,

k) significant alterations of the formulations,

l) storage conditions,

m) trial procedures for the active substance,

n) trial procedures for the investigational medicinal product,

o) trial procedures for non-monographed ancillary substances.

If the amended aspects are furthermore covered by the description in the IMPD, no authorisation is required for this purpose. The cases illustrated in the following **Table 1** for chemically defined substances or herbal substances should exemplify the differentiation between amendments requiring authorisation and amendments not subject to authorisation. The examples are listed

merely for purposes of orientation; they are not purported to be complete. The German competent authority should be consulted in case of doubt.

Table 1: Examples for amendments to the IMP documentation for investigational medicinal products with chemically defined or herbal active substances

ENTR/CT 1 Addendum 5	**Relevance for Quality/safety?**		**Examples**	
Amendment to quality	Yes	Possibly	Authorisation **not** necessary	Authorisation **necessary**
Importation of the investigational medicinal product		●		Amendment of the importing branch
Name or code of the investigational medicinal product		●		Change of the company code to INN or trade name during an ongoing study (amendment of the labelling)
Primary means of packaging		●	Change between means of packaging which were filed as possible alternatives in the IMPD (for example Blister -> HDPE bottle)	Introduction of a new means of packaging
Active substance manufacturer	●		Different production facilities within a single company whereby the specifications remain unchanged	Change to other / new manufacturer
Manufacturing procedure of the active substance		●	Alteration in the synthesis of the initial steps (before GMP starting material) Modification of the process parameters (same procedure, same reagents) Scale-Up	Other synthesis rout (final steps), appearance of a new / additional impurity[16], Expansion of the acceptance criteria, alteration of the physical-chemical properties influencing the quality of the active substance (for example particle size distribution, polymorphy, etc.), alterations in the manufacturing procedure of herbal substances or preparations
Active substance specifications		●		Expansion of the acceptance criteria Deletion of trial items
Manufacturing procedure of the investigational medicinal product		●	Modification of the process parameters (same manufacturing principle)	Significant amendments to the manufacturing procedure (for example dry compaction→ wet granulation, conventional granulation → fluidised bed granulation)

[16] The expansions of the specifications for individual impurities are to be evaluated in consideration of their toxicological harmlessness.

Investigational medicinal product specifications		●		Expansion of the acceptance criteria with possible clinical relevance, for example alteration of hardness with simultaneous influence on decomposition time and/or the in vitro release of the active substance; deletion of trial items
Specification of ancillary substances with potential influence on the properties of the product	●			For example: Alteration of the particle size distribution with influence on the in vitro release of the active substance
Period of usability including stability after opening		●	Extension of the period of usability, broadening of the storage conditions on the basis of additional data with lifespan specifications remaining unchanged	Shortening of the period of usability, narrowing of the storage conditions
Significant alterations of the formulations	●		Qualitatively identical but quantitatively different composition of tablet lacquer with non-functional coating, different form of IR tablet	Altered composition (including exchange of ancillary substances for alternatives of identical function; for example different disintegrant)
Trial procedures for the active substance		●	Variation of the methods in the scope of the IMPD. New analysis conditions are validated and deliver equivalent or better validation results	Implementation of other analysis procedures (for example NIR instead of HPLC)
Trial procedures for the investigational medicinal product		●		
Trial procedures for non-monographed ancillary substances		●		

2. Subsequent amendments to statements on preclinical investigations

a) findings of new preclinical investigations, if they require an amendment of the risk assessment,

b) new interpretations of findings from previously submitted preclinical investigations, if they necessitate an amendment to the risk assessment.

3. Subsequent amendments to statements on clinical investigations

a) safety-relevant findings from clinical investigations or from the application of the investigational medicinal product in humans,

b) safety-relevant findings of new clinical/pharmacological investigations or new interpretations of data from previously conducted clinical/pharmacological investigations,

c) safety-relevant findings of new clinical trials or new interpretations of the findings of previously conducted clinical trials,

d) amendments to the Investigator's Brochure which could influence the classification of SUSARs.

4. Subsequent amendments to the trial protocol

a) study design,

b) inclusion and exclusion criteria,

c) proof of efficacy,

d) safety parameters,

e) test parameters,

f) number and scheme of sample drawings

g) amendments to the stopping criteria, for both individual participants as well as the complete clinical trial,

h) change of the end of the clinical trial as defined in the trial protocol.

5. Subsequent amendments to the organisation of the clinical trial

a) Change of the coordinating investigator of the clinical trial in multicentric clinical trials or change of the principal investigator or investigator in monocentric clinical trials,

b) Change of the sponsor or his representative,

c) Change of a clinical research organisation (CRO) involved.

VIII. Interruption, completion and summary of the report

1. Declaration of the interruption or the end of a clinical trial

The end of the clinical trial is to be defined in the trial protocol to be submitted with the request for authorisation according to **§ 42 AMG**. As a rule, it is the date of the final visit to the investigator of the last subject included in the trial in connection with the clinical trial. Amendments to this determination are subject to authorisation. The declaration is to be carried out by the sponsor within 90 days if the trial is concluded as scheduled; within 15 days if the trial is concluded ahead of schedule. The reasons for a premature completion are to be explained clearly.

The following is to be announced:

a) the completion of the clinical trial in all trial centres in Germany,

b) the completion of the clinical trial in all trial centres worldwide, as soon as the information is available (see **ENTR/CT 1** Section 4.3.3).

The announcement of the completion or interruption of a clinical trial should contain the statements provided in guideline **ENTR/CT 1** under Section 4.3.3 and be carried out with the use of the form in Annex 3 of **ENTR/CT 1**.

In the event of premature completion of the clinical trial, the following information should be supplemented:

a) reasons for the premature completion or interruption of the clinical trial,

b) number of persons affected who were included in the clinical trial up to this point in time and treated with the investigational medicinal product(s),

c) suggested measures regarding patients still undergoing treatment at the point in time of the completion or interruption of the clinical trial.

2. Summary of the report on the clinical trial upon its completion

Within one year of the completion of the clinical trial in all countries involved, the sponsor is to deliver a summary of the report on the clinical trial to the German competent authority, which is to cover all the significant findings of the clinical trial (**§ 13 para. 9 GCP-V**). As far as possible, the summary of the report should be structured according to **Annex 1 of the Note for guidance on structure and content of clinical study reports (CMP/ICH/137/95**).

IX. Glossary

AMG	German Medicines Act (*Arzneimittelgesetz*)
AMGKostV	AMG Cost Ordinance (Arzneimittelkostenverordnung)
BfArM	Federal Institute for Drugs and Medical Devices; German competent authority for medicinal products and medical devices (*Bundesinstitut für Arzneimittel und Medizinprodukte*)
BOB	German competent authority (*Bundesoberbehörde*)
BtMG	German Narcotics Act (*Betäubungsmittelgesetz*)
EDQM	European Directorate for the Quality of Medicines
EMEA	European Medicines Agency (previously European Agency for the Evaluation of Medicinal Products)
CHMP	Committee for Medicinal Products for Human Use (previously CPMP)
CPMP	Committee for Proprietary Medicinal Products
CTD	Common Technical Document, Notice to Applicants, Volume 2B, Medicinal Products for Human Use, Presentation and Content of Dossier
GCP	Good Clinical Practice
GCP-V	Good Clinical Practice statutory regulation in accordance with § 42 para. 3 *AMG*
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
Request for Authorisation	Request for the authorisation of a clinical trial of pharmaceuticals for human use from the competent higher federal authority
EudraCT Databank	European databank of clinical trials
EudraCT Number	Number under which every clinical trial conducted in a member state of the European Union is registered in the EudraCT Databank. The EudraCT number is assigned one time for each clinical trial taking place in an EU member state, and under this number, the applicable clinical trial is registered in the EudraCT Databank. Even in cases of multinational, multicentric trials, the same number applies for each member state in which at least one trial site takes part in the clinical trial.
IB	Investigator's Brochure

EWR	European Economic Area, EEA (*Europäischer Wirtschaftsraum*)
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
INN	International Non-proprietary Name According to the policies created and confirmed by WHO, a name which cannot be trademarked according to trademark law
IUPAC Nomenclature	Nomenclature of the International Union of Pure and Applied Chemistry on the chemical designation of substances
JP	Japanese Pharmacopoeia
MedDRA	Medicinal Dictionary for Regulatory Activities
MRA	Mutual Recognition Agreement
NOEL	No Observed Effect Level
NOAEL	No Observed Adverse Effect Level
PEI	Paul Ehrlich Institute - German competent authority for sera and vaccines
Ph. Eur.	European Pharmacopoeia
Trial Protocol Code	Alphanumeric code of the trial protocol determined by the sponsor
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
USP	United States Pharmacopoeia

X. Index of directives and guidelines cited

Directive 2001/20/EC	Directive 2001/20/EC of the European Parliament and Council of April 4th 2001 on the approximation of legal and administrative regulations of the member states on the use of good clinical practice in the implementation of clinical trials with pharmaceuticals for human use (filing no. L 121/34 from 01.05.01)
Directive 2003/63/EC	Directive 2003/63/EC of the Commission of June 25th, 2003 for the amendment of Directive 2001/83/EC of the European Parliament and Council on the creation of a community codex for pharmaceuticals for human use (filing no. L 159 from 27.06.03, pg. 46; amended L302 2003 pg. 40)
Directive 2002/98/EC	Directive 2002/98/EC of the European Parliament and Council of January 27th 2003 on the determination of quality and safety standards for the recovery, testing, processing, storage and distribution of human blood and blood components and for the amendment of Directive 2001/83/EC
Guideline ENTR/CT 1	Detailed guidance for request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial; Revision 2, October 2005
Guideline ENTR/CT 2	Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use, Revision 1, February 2006.
Guideline ENTR/CT 3	Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use, Revision 2, April 2006
Guideline ENTR/CT 5	Detailed guidance on the European clinical trials database (EudraCT Database) April 2003: This guideline is supplemented by: a) Guideline ENTR/CT 5.1 Amendment describing deployment of EudraCT – Lot 1 for May 2004 b) Guideline ENTR/CT 5.2 Annex to CT 5.1 describing deployment of EudraCT – Lot for May 2004 Core dataset
CPMP/ICH/135/95	Note for guidance on good clinical practice
CPMP/ICH/137/95	Note for guidance on structure and content of clinical study reports
CPMP/ICH/140/95	Note for guidance on the need for carcinogenicity studies of pharmaceuticals
CPMP/ICH/141/95	Note for guidance on genotoxicity: Guidance on specific aspects of regulatory genotoxicity tests for pharmaceuticals
CPMP/ICH/174/95	Note for guidance on genotoxicity: A standard battery for genotoxicity testing of pharmaceuticals

CPMP/ICH/286/95	Note for guidance on non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals
CPMP/ICH/291/95	Note for guidance on general considerations for clinical trials
CPMP/ICH/300/95	Note for guidance on duration of chronic toxicity testing in animals (rodent and non-rodent toxicity testing)
CPMP/ICH/302/95	Note for guidance on preclinical safety evaluation of biotechnology derived pharmaceuticals
CPMP/ICH/365/95	Note for guidance on specifications: Test procedures and acceptance criteria for biotechnological/biological product
CPMP/ICH/378/95	Note for guidance on dose response information to support product registration
CPMP/ICH/379/95	Note for guidance on studies in support of special populations: geriatrics
CPMP/ICH/384/95	Note for guidance on toxicokinetics – The assessment of systemic exposure in toxicity studies
CPMP/ICH/385/95	Note for guidance on pharmacokinetics – Guidance for repeated dose tissue distribution studies
CPMP/ICH/386/95	Note for guidance on specific reproductive toxicology: Detection of toxicity to reproduction for medicinal products
CPMP/ICH/539/00	Note for guidance on safety pharmacology studies for human pharmaceuticals
CPMP/EWP560/95	Note for guidance on the investigation of drug interactions
CPMP/EWP/QWP/1401/98	Note for guidance on the investigation of bioavailibility and bioequivalence
CPMP/ICH/2711/99	Note for guidance on clinical investigation of medicinal products in the paediatric population
CPMP/SWP/398/01	Note for guidance on photosafety testing
CPMP/SWP/997/96	Note for guidance on the pre-clinical evaluation of anticancer medicinal products
CPMP/SWP/1042/99	Note for guidance on repeated dose toxicity
CPMP/SWP/2145/00	Note for guidance on non-clinical local tolerance testing of medicinal products
CPMP/SWP/2599/02/Rev 1	Position paper on non-clinical safety studies to support clinical trials with a single microdose

CPMP/EMEA/CHMP/SWP/258/498/2005, draft

	Guideline on the non-clinical development of fixed combinations of medicinal products
EMEA/CHMP/SWP/169215/2005,draft	Guideline on the need for non-clinical testing in juvenile animals on human pharmaceuticals for paediatric indications
EMEA 410/01/Rev. 2	TSE guideline, Official Journal of the European Union C24 from 28.01.2004
F2/BL D(2003) Revision 1 (GMP Annex 13)	Volume 4 Good Manufacturing Practices, Annex 13 -Manufacture of investigational medicinal products, July 2003
EudraLex 2C	Notice to applicants, 2C, a guideline on summary of product characteristics, December 1999
EudraLex 3BS11A	Note for guidance on pharmacokinetics and metabolic studies in the safety evaluation of new medicinal products in animals
EudraLex 3CC3A	Note for guidance on pharmacokinetic studies in humans
EudraLex 3CC29A	Note for guidance on investigation of chiral active substances

Appendices to Section II

Appendix II / 1

Table 2: Simplified IMPD in subject to authorisation status as well as further particularities of the investigational medicinal product

Authorisation status, further particularities of the investigational medicinal product	Pharmaceutical Quality Data	Preclinical Data	Clinical Data
1. The investigational medicinal product is authorised in an EU member state:			
a) the application in the clinical trial is carried out within the conditions of authorisation (SmPC)	SmPC	SmPC	SmPC
b) the application in the clinical trial is carried out outside of the conditions of authorisation	SmPC	Required where applicable	Required where applicable
c) the investigational medicinal product has been supplied by a different manufacturer	Data on active substance as well as investigational medicinal product	SmPC[17]	SmPC
d) a pharmacologically active substance contained in the investigational medicinal product has been supplied by a different manufacturer	Data on active substance as well as investigational medicinal product	SmPC	SmPC
e) the investigational medicinal product has been blinded	Data on investigational medicinal product	SmPC	SmPC
2. A different pharmaceutical form or strength of the investigational medicinal product is authorised in an EM member state	Data on investigational medicinal product	Required	Required
3. The investigational medicinal product is not authorised in an EU member state, but the active substance it contains is authorised in an EU member state as pharmacologically active component and			
a) is supplied by the same manufacturer	Data on investigational medicinal	Required	Required

[17] As soon as the alteration of the manufacturing process for the active substance results in new potentially toxic substances, impurities or degradation products, or if a new material is introduced in the manufacture of biological products, supplemental information from preclinical investigations may be required.

	product		
b) is supplied by a different manufacturer	Data on active substance as well as investigational medicinal product	Required	Required
4. A clinical trial for the investigational medicinal product has previously been authorised by the BOB[18]:			
a) no new data is available since authorisation by the BOB	No new data required	No new data required	No new data required
b) new data is available since authorisation by the BOB	New data	New data	New data
5. The investigational medicinal product is a placebo	Data on investigational medicinal product	Not required	Not required

For investigational medicinal products authorised only within one state in the ICH (International Conference on Harmonisation) or EAA region, the information in under Item 1 in **Table 2** largely applies. In these cases, a certified translation of the SmPC or comparable official document in German or English may be submitted, if this official document corresponds at least to the requirements of the SmPC (see **Notice to applicants. 2C, A guideline on summary of product characteristics, December 1999**).

In addition, the requirements in **Appendix III / 4** are to be observed[19] and corresponding documents, where applicable, are to be submitted. The competent federal authority is unconditionally to be contacted in advance for biologically/biotechnically manufactured active substances.

Appendices to Section III

Appendix III / 1

For investigational medicinal products to be used in clinical trials in accordance with Appendices **III / 1**, **III / 3** and **III / 4**, a reference to a monograph of the European Pharmacopoeia (Ph. Eur.), the pharmacopoeia of an EU member state, the United States Pharmacopoeia (USP) or to the Japanese Pharmacopoeia (JP) will be accepted.

For investigational medicinal products in generic bioequivalence trials intended to support a request for authorisation in the EU, care should be given that the Ph. Eur. requirements are met.

[18] In the event of a reference to documents submitted by a different applicant to the German competent authority in an authorisation procedure, a certificate of this applicant is to be submitted stating the applicant's approval of the reference and confirming that the required documents have been provided to the new applicant.

[19] However, the proof of identity listed there is only to be submitted upon request of the Germana competent authority.

General requirements for the chemical/pharmaceutical and biological documentation for investigational medicinal products for clinical trials in phases I-III to be submitted with the request for trial authorisation.

2.1. S Active substance

2.1. S.1 General statements

2.1. S.1.1 Nomenclature

Information concerning the nomenclature of the active substance is to be provided (for example, proposed INN designation, pharmacopoeia/chemical name, company/laboratory code or other names or codes).

In the case of gene transfer pharmaceuticals, statements are to be provided on the designation and origin of the therapeutic gene and of the vector used.

The isotope (IUPAC nomenclature) is to be specified for radionuclides.

Mother as well as daughter nuclides are active substances in radionuclide generators. In kits for labelling, the part of the formulation which will carry or bind the radionuclide is to be considered the active substance,and is labelled product is to be named. For organic/chemical precursors, requirements analogous to those for active substances apply.

For herbal substances, the binomial scientific name of the plant (genus, species, variety and author) and, if applicable, the chemotype, as well as parts of the plant, the definition of the herbal substance, further names (synonyms mentioned in other pharmacopoeias) and the laboratory code number are to be stated.

For herbal preparations, the ratio of the herbal substance to the herbal preparation and the solvents used for the extraction are additionally to be specified.

2.1. S.1.2 Structure

The data available at the respective stage of development is to be submitted.

In particular, this includes structure formulas, molecular weight and statements on chirality/stereochemistry, to the extent elucidated at this point in time.

For biological products and biotechnologically manufactured peptides and proteins, the primary structure as well as the structure of higher order are to be submitted, to the extent determined at this time, as well as the molecular weight, the post-translational modifications and other modifications, if applicable.

In the case of gene transfer medicinal products, detailed statements, according to the type of the medicinal product, are necessary on the vector used, regulatory sequences, packaging signals, resistance genes and plasmid structure (plasmid map and sequence). The complete sequence of the gene to be transferred, as well as the vector, is to be submitted. If an ex-vivo gene transfer is to be conducted, specifications on the type and origin of the modified cells shall be required.

For radionuclide kits, the structure formula of the ligands before, and, if known, after the radio labelling is to be submitted.

For herbal substances and herbal preparations, physical state, extract type, and constituent(s) or lead compound(s) determining the efficacy are additionally to be submitted. Statements on the excipients are to be provided.

2.1. S.1.3 General properties

Physicochemical and other relevant properties of the active substance are to be listed. In particular, melting point, polymorphism, solubility profile, pH/pKa values, hygroscopicity, are to be listed here, to the extent applicable.

Specifications on the particle size distribution of the active substance are to be submitted if they influence the quality or processability of the investigational medicinal product.

Biological activity is to be described for biologically/biotechnologically manufactured substances.

In the case of gene transfer pharmaceuticals, statements on the titer, tropism and particle count of viral vectors are necessary, where applicable.

Physical properties are to be specified for radionuclides.

2.1. S.2 Manufacturing

2.1. S.2.1 Manufacturer

The name and address of all manufacturer/s and, if different, the manufacturing site as well as the responsible site for the batch release are to be specified. The name and address of the importer(s), if applicable, are also to be submitted.

For radiopharmaceuticals, the manufacturer of the radionuclide, radiolabelled and other labelled precursors already labelled as well as organic-chemical precursor substances are to be specified.

2.1. S.2.2 Description of the manufacturing process and the process inspection

For chemically defined active substances:

A summary and flow chart of the synthesis or manufacturing process stating the name of the starting material for the synthesis, intermediates, solvents, catalysts and reagents for the applicable steps are to be submitted. A detailed description is required for particularly critical process steps.

The stereochemical properties of the starting materials for the synthesis are to be discussed if applicable.

For biologically and biotechnologically manufactured active substances, a summarised description of the process and a flow chart of all sequential process steps (upstream/downstream) are to be submitted. The in-process inspections are to be stated in detail. It should begin with the starting materials (for example plasma, cell bank, if available). The scale for the fermentation as well as purification are to be submitted. The definition of a batch is to be specified.

For radionuclides, the corresponding nuclear manufacturing routes including undesired conversions are to be described. The conditions for irradiation are to be listed.
In addition, statements on the purification or segregation processes for the radiopharmaceutical and the organic-chemical precursors are required where applicable. In special cases, statements on the possible consequences of incomplete labelling or in-vivo dissociation of the labelled product are also required.

For herbal substances or preparations, a summary and flow chart of the successive steps beginning with the plant cultivation or drug collection up to the active substance batch obtained are to be submitted. The in-process controls are to be documented. The main steps of the manufacturing process are to be indicated.

Productions scale and batch size are to be specified in all of the above-mentioned cases. If the synthesis or manufacture of the batches iused for the non-clinical safety trials deviates from the batch(es) used in the clinical trials, a flow chart for the manufacture of the batches for the non-clinical safety trials is to be submitted.

2.1. S.2.3 Control of materials

Production cell line

Summarised information on the origin, history and establishment of the cell lines implemented is to be submitted. The composition and characterisation of the introduced or altered nucleic acids are to be described.

Cell bank system

The cell bank system, its creation and the qualification are to be described briefly. 'Master cell bank', 'working cell bank', and, if applicable, production cell lines are to be characterised and the tests including specifications are to be listed in tabular form.

Raw materials

For biologically and biotechnologically manufactured active substances, the raw materials and starting materials used are to be named. It is to be specified for each item whether it is pharmacopoeia quality.

Raw and starting materials of human and animal origin are to be labelled, and documents on virus safety are to be attached (see Appendix 2.1.A.2).

For sera and blood preparations, the quality of the plasma according to **Directive 2002/98/EC** is to be documented.

2.1. S.2.4 Control of critical manufacturing steps and intermediate products for biologically or biotechnologically manufactured active substances

For biologically or biotechnologically manufactured active substances, the in-process controls of critical manufacturing steps conducted are to be documented. Intermediates, including the quality control tests, are to be specified.

Should intermediates be stored and not immediately tested before further use, the storage period and storage conditions for the phase I clinical trials are to be specified and correspondingly justified.

Supplements for clinical trials in phases II and III:

If the storage or lifetimes for intermediate products are provided, the storage duration and storage conditions for clinical trials in phases II and III are to be specified and corresponding stability data is to be submitted.

2.1. S.2.5 Process validation and/or evaluation for biologically or biotechnologically manufactured active substances

For biologically and biotechnologically manufactured active substances, the already submitted information on process validation is to be listed.

2.1.2.6 Development of the manufacturing process for biologically or biotechnologically manufactured active substances

The already available information on process validation is to be presented for biologically and biotechnologically manufactured active substances.

2.1. S.3 Characterisation

2.1. S.3.1 Elucidation of the structure and other characteristics

For chemically defined active substances, a summarised description of the results of the examinations of structure and of other characteristics (e.g. NMR, mass spectroscopy, UV and IR spectrums) with attachments of a typical spectrum or other findings (example.g. a copy of a DSC process) are to be submitted.

For biologically and biotechnologically manufactured active substances, all available information on proof of structure, including post-translational or other modifications and the biological activity are to be summarised. The microheterogeneity and modifications of the substance ('product related substances' according to the **Note for guidance on specifications: Test procedures and acceptance criteria for biotechnological/biological products (CMP/ICH/365/96)**) are to be included. The methods used in the characterisation are to be named.

For gene transfer medicinal products, detailed statements on the vector used, regulatory sequences, packaging signals, resistance genes, plasmid scaffold (plasmid map and sequence) are necessary, according to the type of the medicinal product. The complete sequence of the gene to be transferred, as well as the vector, is to be submitted. If an ex-vivo gene transfer is to be conducted, specifications on the type and origin of the modified cells are required.

For radiopharmaceutical active substances, the analogous non-radioactive substances are to be used in the structure determination.

For herbal substances, information on botanical, macroscopic, microscopic and phytochemical characterisation, and, where applicable, on biological activity, are to be submitted. For herbal preparations, statements on phytochemical and physicochemical characterisation, and, if required, on biological activity as well, are to be submitted.

2.1. S.3.2 Impurities

For chemically defined substances, impurities as well as possible degradation products and solvent residues from the synthesis or manufacturing process relevant to the clinical trial or from the starting materials are to be specified.

The consistency of the impurity profiles between the batches used in the respective studies (non-clinical and clinical studies as well as the examinations on proof of quality and safety) is to be evaluated. The solvents and catalysts implemented in each case are also to be taken into account. In the case of deviations, possible influence on the safety of the application is to be discussed.

For biologically and biotechnologically manufactured active substances, impurities are to be determined quantitatively. Impurities originating from the process are to be taken into account, for

example cell substrata (host cell DNA, host cell proteins), from the cell culture (components of the medium, antibiotics), from the purification process (such as column bleeding, virus deactivation residue) and those originating from the active substance, such as precursor and degradation products (for example fragments, dimers, aggregates, oxidised and deamidised proteins). If exclusively qualitative data is submitted for individual impurities, this is to be justified.

An evaluation of the depletion potential of the purification process for the respective impurity is to be undertaken.

For cell preparations, the cells present as impurities are to be characterised and quantified.

For active substances that are radiopharmaceuticals, the radionuclidic, radiochemical and chemical purity is to be described.

For herbal substances and herbal preparations, specifications are to be made on potential contamination with microorganisms, products of microorganisms, pesticides, toxic metals, radioactive contamination, fungicides, etc.

2.1. S.4 Control of the active substance

2.1. S.4.1 Specification

The specifications, their criteria and the tests used are to be submitted for the batch(es) of active substances used in the clinical trial.

Upper limits are to be set for impurities. They can be preliminary and have to be reviewed and, if necessary, adjusted during the development. The safety of use is to be taken into account in the establishment of these limits.

For drug substances which are used in aseptically manufactured medicinal products, an acceptance criterion for microbiological quality is to be determined.

For drug substances that are radiopharmaceuticals, the radioactivity and the time of calibration are to be specified.

Additional information for phase II and phase III clinical trials:
Specifications and acceptance criteria set for previous phase I or phase II trials are to be reviewed and adjusted if necessary to the current stage of development.

2.1. S.4.2 Analytical procedure
The analytical methods used for the active substance are to be provided (e.g. reverse-phase-HPLC, potentiometric titration, head-space-GC, SDS-PAGE, ELISA etc.)
The applied analytical methods for testing the active substance for biological and biotechnological IMPs are to be specified and briefly described.
In addition, for radiopharmaceutical active substances, the procedure for measuring radioactivity is to be described.

2.1. S.4.3 Validation of analytical procedures
For phase I clinical trials, the suitability of the analytical method is to be described briefly. The planned acceptance limits (e.g. for the validation of the parameter ”determination limit for impurities”) and validation parameters (e.g. specificity, linearity, operational range, accuracy, precision, detection and quantification limits) are to be specified in tabular form. The methodology as described in the respective ICH guidelines should be applied.

Additional information for phase II clinical trials:
The suitability of the analytical procedure is to demonstrated. The validation of specific parameters of the testing procedure, carried out following the methodology recommended in the ICH guidelines, is to be specified in tabular form (e.g. values or respectively results for the specificity, linearity, operational range, accuracy, precision, detection and quantification limits).
It is not required that the validation data be presented as a report.

Additional information for phase III clinical trials:
In addition to the requirements for phase II clinical trials, a full validation report is to be kept and to be provided when requested.

2.1. S.4.4 Batch analysis
Batch results or certificates of analysis are to be provided for the active substance batches used in non-clinical studies and for representative active substance batches used in clinical trials. The batch number, batch size, manufacturing site, manufacturing date, testing methods, acceptance criteria and test results are to be listed. In addition, each batch is to be assigned to the synthesis process and/or manufacturing process respectively as specified in 2.1.S.2.2.
Should the manufacturing process vary or differ from one another, the possible effect on the application safety of the IMP is to be discussed. If available, this data is to be provided for the active substance batch(es) to be used in the current clinical trial.
Information regarding all active substance batches, their use, specifications, manufacturing process details, batch number, batch size, manufacturing site, testing methods, and acceptance criteria is to be provided for all biologically/biotechnologically produced IMPs.

2.1. S.4.5 Justification of specifications
The selected specification for impurities is to be briefly justified.

2.1. S.5 Reference standards or materials
Where applicable, the parameters characterising the batch of the drug substance established as the primary standard is to be provided. Furthermore, where applicable, details regarding the establishment of working standards for the quantitative determination of the substances and the impuries are to be included.
The details of the calibration standard and the non-radioactive (cold) standards are required for radioactive materials.

For herbal preparations, the primary reference standards and, if the original drug is not generally known, the herbarium examples are to be fully characterised.

2.1. S.6 Container and closure system
The immediate packaging material used for the active substance is to be specified.

2.1. S.7 Stability
Stability data available at the respective current stage of development is to be summarised in tabular form. Parameters critical to the stability of the drug substance are to be identified e.g. through stress tests and studies under accelerated conditions.
For biologically and biotechnologically produced active substances, the storage period until further processing must be covered by data pertaining to the selected storage conditions.

2.1. P Investigational medicinal product
2.1. P.1 Description and composition of the IMP
The complete qualitative and quantitative composition of the IMP is to be specified. A short description of the dosage form including specification of the function of individual excipients is to be provided.
Additionally, the radioactivity per reference unit is to be specified for radiopharmaceuticals.

2.1. P.2 Pharmaceutical development
The pharmaceutical development of the formulation is to be presented briefly. In the process, new dosage forms and/or excipients are to be justified respectively. In early developmental stages, there may not necessarily be any information or there may be limited information which can be provided in this section. In as far as it is applicable; the compatibility with solvents used for reconstitution, diluents or admixtures is to be verified.
For biologically and biotechnologically produced IMPs, the pharmaceutical development as well as the development of the manufacturing process should be briefly described. For radionuclide kits, the suitability of the method used for radio-labelling is to be demonstrated for the intended use (including test results for physiological distribution as well). For radionuclide generators, the suitability of the elution agent is to be demonstrated.
For radiopharmaceuticals, it is also necessary to provide proof that the planned radioactivity concentrations do not lead to radiolysis.

Additional information for phase II and phase III clinical trials:
Changes to the formulation and/or changes to the dosage form, respectively, compared to the IMP used in earlier clinical trials are to be described. In particular in this case, the possible influence of changes to clinically relevant quality parameters specific to the dosage form is to be discussed, e.g. in vitro dissolution rate
.
2.1. P.3 Manufacture

2.1. P.3.1 Manufacturer
The name and address of the sites involved in manufacturing and testing are to be provided. If multiple manufacturers contribute to the manufacturing of IMP, their respective responsibilities are to be stated clearly.

2.1. P.3.2 Batch formula
The batch formula for the batch to be used in the clinical trial is to be provided. Where relevant, an appropriate range of batch sizes shall be given.

2.1. P.3.3 Description of the manufacturing process and process control
A flow-chart is to be provided depicting the individual manufacturing steps and the components used for each step. In addition, a short description of the manufacturing processes is to be

included. Non-standard manufacturing processes, new technologies and if necessary, new packaging processes are to be described in detail.
A flow-chart clearly depicting the individual manufacturing steps, in-process controls including limits and the components used for each step, is to be provided for biologically and biotechnologically manufactured IMPs. An additional short description of the manufacturing process is to be included.

Additional information for phase II and III clinical trials
Changes to the manufacturing process or the in-process controls compared to those for the manufacture of test compounds used in phase I and/or phase II respectively are to be presented and described. In particular, the possible influence of changes to clinically relevant quality parameters specific to the dosage form are to be discussed, e.g. dissolution rate.

2.1. P.3.4 Controls of critical manufacturing steps and intermediates
Data is not required for IMPs with chemically defined active substances for phase I or phase II clinical trials. Exceptions are:
a) Non-standard manufacturing processes
b) Manufacturing processes for sterile products
For biologically or biotechnologically manufactured IMPs, in-process controls performed for critical manufacturing processes are to be documented.
Intermediates are to be specified including the quality controls performed.
If intermediates are stored, the storage period and storage conditions are to be specified and correspondingly justified.

Additional information for phase III clinical trials:
The critical manufacturing steps, the controls carried out, as well as possible intermediates are to be documented. If storage or standing times are intended for intermediates, the storage period and storage conditions are to be specified and correspondingly justified.

2.1. P.3.5 Process validation and/or evaluation
Process validation data is not required for IMPs that are chemically defined or are plants or plant preparations.
Exceptions are sterilisation processes which are not described in the Ph. Eur., USP or JP. In these cases, the critical manufacturing steps as well as the validation of the manufacturing process are to be presented in a summarised manner and the test methods for in-process controls are to be specified.
For biologically and biotechnologically manufactured IMPs, the information already available regarding the process validation is also to be listed.

2.1. P.4 Controls of excipients

2.1. P.4.1 Specifications
Reference should be taken to a pharmacopoeia monograph as listed under 2.1.P.4.1. For excipients which are not described in any of the above-mentioned pharmacopoeias, the specifications are to be listed and corresponding certificates of analysis are to be submitted.

2.1. P.4.2 Analytical procedure
For excipients which are not described in any of the above-mentioned pharmacopoeias, the analytical methods applied are to be specified.

2.1. P.4.3 Validation of analytical procedure
No documentation is required.

2.1.P.4.4 Justification of specifications

Selected specifications are to be justified for excipients which are not recorded in a monograph as detailed under 2.1.P.4.1.

2.1. P.4.5 Excipients of human or animal origin
See Attachment III / 1, Attachment 2.1.A.2.

2.1. P.4.6 Novel excipients
Detailed information regarding the manufacturing process, characterisation and control as well as product safety is to be provided for novel excipients. The details listed in the CTD structure under 2.1.S. are to be provided.

2.1. P.5 Control of the investigational medicinal product

2.1 .P.5.1 Specifications
The chosen specification, i.e. the release and shelf-life specifications are to be specified including test method information and corresponding acceptance criteria. Upper limits are to be specified for impurities; these can be provisional and can be reviewed and correspondingly adjusted if necessary during further development. Safety considerations are to be taken into account when establishing these limits.
For radiopharmaceuticals, it is necessary to specify which tests are performed before release and which will be carried out retrospectively. Appropriate tests after radiolabeling are to be taken into account for radionuclide kits.

Additional information for phase II and phase III clinical trials:
The limits established within the scope of phase I and/or phase II trials respectively are to be reviewed and adjusted corresponding to the current development stage where appropriate.

2.1. P.5.2 Analytical procedure
The analytical procedures are to be specified (e.g. dissolution test method).
For complex, innovative pharmaceutical forms, a greater level of detail may be necessary.

2.1. P.5.3 Validation of analytical procedures
The suitability of the analytical methods for phase I clinical trials is to be described briefly. The planned acceptance limits (e.g. for the validation of the parameter “quantification limit of the impurities”) and validation parameters (e.g. specificity, linearity, operational range, accuracy, precision, detection and quantification limits) are to be specified in tabular form. The methodology described in the ICH guidelines is to be taken into consideration in this case.

Additional information for phase II clinical trials:
The suitability of the analytical method is to be demonstrated. The validation of specific parameters of the respective analytical method carried out following the methodology recommended in the ICH guidelines are to be specified in tabular form (e.g. values and/or results respectively for the specificity, linearity, the range, the accuracy, precision, detection and quantification limits).
It is not necessary to provide validation data as a report.

Additional information for phase III clinical trials:
In addition to the requirements for phase II clinical trials, a complete validation report is to be kept and to be provided when requested.
In a variation of this requirement, summaries of validation reports are to be provided for biologically/ biotechnologically manufactured products.

2.1. P.5.4 Batch analyses

Batch results or certificates of analysis for batches representative of the IMPs to be used in clinical trials are to be provided. The batch number, batch size, manufacturing site, manufacturing date, test methods and acceptance criteria are to be submitted.

For biologically/biotechnologically produced products, information on all batches, their use, the specifications, the manufacturing process, the batch number, batch size, manufacturing site, manufacturing date, the test methods and acceptance criteria are to be submitted.

2.1. P.5.5 Characterisation of the Impurities

Impurities must be documented in so far as they deviate from the details given under 2.1.S.3.2 of this chapter.

2.1. P.5.6 Justification for the Specifications

For IMPs in Phase 1 of clinical trials, a brief description of the reasons for choosing the specifications in regard to the impurities is sufficient. Where appropriate, an explanation of the toxicological reasons must be given.

Additional information for clinical trials in the phases II and III:

A brief statement to substantiate the chosen specifications must be given. Changes of the specifications compared with the previous specifications are to be explained. Toxicological reasons have to be presented, if applicable.

2.1. P.6 Reference Standards or Reference Materials

If applicable, the characteristics of the batch of the active substance shall be submitted which are established as the respective primary reference standard. Furthermore, if applicable, details shall be submitted of the work standards applied in determining the contents and in conducting the purity test of the batches listed under 2.1.P.5.4 of this chapter. If applicable, reference may be made to 2.1.S.5 of this chapter.

2.1. P.7 Container and Closure System

Details of the container and sealing system used in the clinical trials of the investigational new drug and, if applicable, for the reconstitution solutions shall be stated. If materials are used that are described neither in the Ph. Eur., nor in a pharmacopoeia of one of the EU member states, nor in the USP, nor the JP, a description must be submitted with the relevant specifications.

2.1. P.8 Durability

The usability deadline for the duration of the intended clinical studies can be extrapolated in so far as stability studies accompany the examination during the entire duration of the clinical trial. If the possibility of extrapolation is to be used, it must be confirmed that accompanying stability studies will be carried out throughout the trial.
For investigational new drugs after reconstitution, dilution or addition and for investigational new drugs for multiple applications, the stability period after opening the receptacle must be documented. If, however, the investigational new drug is intended for immediate application on humans, the examination of the stability after opening the receptacle may be dispensed with if it can be substantiated that no instabilities influencing the quality of the investigational new drug are to be expected.

For radioactive drugs, the calibration time point must be determined, since the shelf-life results, among other things, from the physical half-life of the radioactive isotope.

For clinical trials in Phase I:

For clinical trials in Phase I, it must be confirmed that accompanying stability studies are carried out and that, prior to commencing the study, at least the examinations under conditions accelerating degradation and conditions of long-term storage will have been initiated. In so far as they are available, the results of these stability studies shall be summarised in the form of a table Supportive data from the development studies shall be summarised and submitted in tabular form. The usability deadline envisaged for the clinical investigational product shall be substantiated on the basis of the data available.

For biologically/biotechnologically manufactured investigational new drugs, the already available results of stability studies shall be submitted as summaries or in tabular form. In substantiated cases, the performance of studies under degradation accelerating conditions may be dispensed with.

Additional data for clinical examinations in the Phases II and III:

The stability data pertaining to the respective stage of development, including the derivation of the usability deadline proposed for the clinical examination, shall be submitted in tabular form. They should comprise at least the results of examinations under conditions accelerating degradation and conditions of long-term storage.

For biologically/biotechnologically manufactured investigational new drugs, the already available results of stability studies shall be submitted as summaries or in tabular form. In substantiated cases, the performance of studies under degradation accelerating conditions may be dispensed with.

2.1. A Annexes

2.1. A.1 Premises and Equipment

Information is necessary only for biologically and biotechnologically manufactured investigational new drugs.

All equipment for manufacturing and testing shall be listed.

It is not expected to conduct a validation of the manufacturing process as comprehensive as at the time of the application for approval; the validation of the premises and equipment, on the other hand, is expected. (Eudralex, Vol . 4, Annex 13, No. 17). During the course of production, data should continue to be collected and evaluated and, if necessary, used for the optimisation of the manufacturing process.

It shall be confirmed that all manufacturing and/or testing equipment is in conformity with GMP requirements and has been inspected by the competent supervisory authority.

2.1. A.2 Evaluation to assess the safety of foreign substances; monitoring of bacteria, mycoplasmae and fungi.

The avoidance and monitoring of bacteria, mycoplasms and fungi with the use of biological substances shall be documented. The relevant information may be placed in the main section under manufacturing process.

TSE Safety Precautions

All raw materials and base materials derived from animal species or similar substances that come into contact with the drug during the production process (including auxiliary materials) shall be identified. For these substances, conformity with the TSE directive (EMEA 410/01/ rev. 2; Gazette of the European Union C24, S. 6-19 dated 28.1.2004 in the respectively applicable version) shall be documented, this may be supported by a corresponding certificate of the *European Directorate for the Quality of Medicines (EDQM)*.

Anti-Virus Precautions

Substances of Biological Origin

All biological raw materials and base materials or substances of biological origin that come into contact with the drug during the production process (including auxiliary materials) shall be identified. Furthermore, these substances shall be evaluated in regard to a possible deactivation or removal of viruses during production and the possible risk of the entry of viruses through said substances shall be discussed (Exception: known auxiliary materials, such as gelatine, which meet the requirements of the Ph. Eur., attested, e.g. by a certificate of the EDQM).

The Testing of Substances of Biological Origin

When using human blood or other human tissue, the careful selection and testing of the donor shall be described. In the case of substances derived from human plasma, reference may be made to a corresponding Plasma Master File. In the case of base materials derived from animal blood or other animal tissue, the epidemiology of the geographic region, the husbandry methods, the veterinary medical monitoring and the specific testing of the animals shall be described. Cell cultures shall be examined for possible contamination by viruses. During this process, attention shall be paid to: contamination by the base tissue, contamination caused by the genetic manipulation of the cells (e.g. cell transformations with EBV, SV40, adenoviruses as well as other helper viruses during gene transfer), contamination by biological auxiliary substances with the cell culture (e.g. trypsin, bovine serum). In the case of vaccines, the examination should be conducted in accordance with the relevant pharmacopoeia monographs.

Examination of the Unprocessed Bulk

As far as applicable, further trials on the unprocessed bulk may be necessary, depending on the raw and base materials, the prior examination of the cell culture and the possibility of contamination during the fermentation phase.

The Testing of the Purified Active Substance and/or of the Investigational New Drug

Testing is not necessary if contamination can be excluded by the characterisation and/or testing of the raw and base materials as described above or by corresponding processes for virus deactivation/removal.

Studies for the Deactivation/Removal of Viruses

According to Eudralex, Vol . 4, Annex 13., the same specified requirements apply to the manufacturing processes for clinical investigational new drugs in regard to the deactivation/ removal of viruses as those which apply to approved drugs. The efficacy of individual production

steps to eliminate viruses shall be substantiated by validation studies. The scope of these studies is to be substantiated under consideration of the risk involved in the raw and base materials/auxiliary materials used in the context of experience gained with certain deactivation/removal methods with standardised manufacturing processes.

Annex III / 2
Requirements for the Chemical, Pharmaceutical, and Biological Documentation for Clinical Investigational New Drugs in Generic Bioequivalence Studies

The following defined requirements apply specifically for investigational new drugs that are to be used as test compounds in bioequivalence studies in accordance with *Note for guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98)* to substantiate the efficacy of generic drugs (Bioequivalence to an approved reference product).

If test compounds in bioequivalence studies are intended to support an application for approval in the EU, it must be ensured that the requirements of the Ph. Eur. are complied with.

2.1. S Active substance

2.1. S.1 General Information

2.1. S.1.1 Nomenclature

Information regarding the nomenclature of the active substance (e.g. INN designation, pharmacopoeia/chemical designation, company/laboratory code or other designation) is to be supplied.

2.1. S.1.2 Structure

The structural formula shall be given.

2.1 .S.1.3 General Characteristics

Physicochemical and other relevant characteristics of the active substance shall be listed.

2.1. S.2 Manufacturing

2.1. S.2.1 Manufacturer

The name and address of the manufacturer(s) and, if different, the place of manufacture as well as the name of the person responsible for releasing the batches shall be given. If applicable, the name and address of the importer(s) shall be supplied.

2.1 .S.2.2 Description of the Manufacturing Process and of the Process Control Procedures.

For active substances whose quality is validated by a monograph of the Ph. Eur., of a pharmacopoeia of an EU member state, or, if unavailable, of the USP or of the JP, no further information is required.
For active substances that are not described in one of the above mentioned pharmacopoeia, a summary of the flow chart of the synthesis or manufacturing process, indicating the base materials used in the synthesis, the intermediate products, solvents, catalysts and reagents for each respective stage of the process shall be submitted. The stereo-chemical characteristics of the base materials of the synthesis, if applicable, shall be discussed.

2.1 .S.3 Characterisation

2.1. S.3.2 Impurities

For active substances whose quality is controlled by a monograph of the Ph. Eur., of a pharmacopoeia of an EU member state, or, if unavailable, of the USP or of the JP, no further information is required.

For active substances that are not described in one of the above pharmacopoeia, impurities and solvent residues from synthesis relevant to the respective clinical trial or manufacturing process and from the base materials shall be given as well as possible pyrolysis products.

2.1. S.4 Control of the Active Substance

2.1 .S.4.1 Specification

For active substances that are to be further processed to aseptically produced compounds, an acceptance criterion for the microbiological quality shall be determined.

For active substances whose quality is sufficiently validated by a monograph of the Ph. Eur., a monograph of a pharmacopoeia of an EU member state, or, if unavailable, of the USP or of the JP, no further information is required.

For active substances that are not described in one of the above mentioned pharmacopoeia, the specifications of the active substance batch(es) to be used in the bioequivalence study applied for shall be submitted, including information on the test method and the respective acceptance criteria.

2.1 .S.4.2 Analytical Methods

For active substances that are not described in one of the pharmacopoeia named under 2.1.S.4.1, the analytical methods used for the active substance shall be given (e.g. reverse-phase HPLC, potentiometric titration, head-space GC, SDS-PAGE, ELISA, etc.).

2.1 .S.4.2 Validation of the Analytical Methods

For active substances that are not described in one of the pharmacopoeia named under 2.1.S.4.1 of this chapter, the suitability of the analytical methods must be substantiated. The parameters of the respective test methods in the framework of the ICH compliant validation shall be submitted in tabular form (e.g. acceptance limits for the validation of the parameters' limit of determination of impurities). A complete validation report shall be kept available for presentation on request.

2.1. S.4.4 Batch Analysis

For the batch(es) to be used in the study, comprehensive analysis certificates shall be submitted, comprising details of the batch designation, batch size, place of manufacture, date of manufacture, corresponding test methods, acceptance criteria as well as the examination results.

2.1. P.5.6 Reasoning for the Specifications

For active substances that are not described in one of the pharmacopoeia named under 2.1.S.4.1 of this chapter, a brief explanation of the reasons for the choice of specifications for the impurities shall be submitted.

2.1. P.5 Reference Standards or Reference Materials

For active substances that are not described in one of the pharmacopoeia named under 2.1.S.4.1 of this chapter, the characterisation characteristics of the active substance batch which is established in each case as the primary reference standard shall be submitted. Information shall

be included concerning the establishment of work standards and on the determination of the contents as well as the purity tests.

2.1.P.7 Container and Sealing System

Details of the primary means of packaging for the active substance shall be given

2.1. S.7 Stability

The available stability data shall be summarised in tabular form.

2.1. P Investigational New Drug

2.1. P.1 Designation and Composition of the Investigational New Drug

The comprehensive qualitative and quantitative composition of the investigational new drug shall be specified.

2.1. P.2 Pharmaceutical Development

A brief description of the pharmaceutical form shall be submitted.

2.1. P.3 Manufacturing

2.1. P.3.1 Manufacturer

The name and address of the companies involved in the manufacturing and testing shall be supplied. In the event that several manufacturers participate in the production of the investigational new drug, their respective fields of responsibility shall be clearly described.

2.1. P.3.2 Batch Formula

The manufacturing formula (formulation) for the batch to be used in the clinical trial shall be specified.

2.1. S.2.2 Description of the Manufacturing Process and of the Process Control Procedures.

A flow chart shall be submitted, clearly showing the individual manufacturing steps and the use of the respective, component substances. In addition, a brief description of the manufacturing method shall be included.

2.1. P.3.4 Control of Critical Manufacturing Steps and Intermediate Products

The critical manufacturing steps, the controls performed as well as any intermediate products that may be involved shall be listed.

2.1. P.3.5 Process Validation and/or Evaluation

Data on the process validation are not required.

An exception to this are sterilisation methods that are not standard methods of the Ph. Eur. In this case, the critical manufacturing steps as well as the validation of the manufacturing method shall be presented in summarised form and the test methods of the in-process controls shall be specified.

2.1. P.4 Control of the Auxiliary Substances

2.1. P.4.1 Specification

If a monograph is available, reference shall be made to the Ph. Eur. or a pharmacopoeia of one of the EU member states. For auxiliary substances that are neither monographed in the above mentioned pharmacopoeia nor in the USP nor in the JP, the specifications shall be listed and submitted together with the pertinent analysis certificates.

2.1 .P.4.2 Analytical Methods

If no reference can be made to one of the pharmacopoeia monographs listed under 2.1.P.4.1 of this chapter, the analytical methods used must be specified.

2.1. P.4.5 Auxiliary substances of Human or Animal Origin

See in Annex III / 1, Annex 2.1.A.2.

2.1. P.4.6 New Kinds of Auxiliary Substances

For new auxiliary substances, detailed information shall be provided concerning the manufacturing process, characterisation and control as well as product safety. The information specified in the CTD structure under 2.1.S. shall be provided.

2.1. P.5 Control of the Investigational New Drug

2.1. P.5.1 Specification(s)

The selected specifications, i.e. release and lifetime specifications shall be specified, giving information on test methods and pertinent acceptance criteria.

2.1. P.5.2 Analytical Methods

Details must be given of the analytical methods (e.g. for the determination of in-vitro release of the active substance).

2.1. P.5.3 Validation of the Analytical Methods

The validation of the analytical methods is to be carried out in accordance with ICH guidelines. A tabular summary of the validation results shall be submitted. A complete validation report shall be kept available for presentation on request.

2.1. P.5.4 Batch Analysis

The analysis certificate(s) for the batch(es) to be used in the bioequivalence study shall be submitted, including details of the batch designation, batch size, place of manufacture, date of manufacture, test methods, acceptance criteria, trial results, batch numbers of the medicinally effective component and the examination results.

2.1. P.5.5 Characterisation of the Impurities

Impurities must be documented in so far as they deviate from the details given under 2.1.S.3.2 of this chapter.

2.1. P.5.6 Substantiation of the Specifications

A brief statement substantiating the chosen specifications shall be given.

Page 45

2.1. P.6 Reference Standards or Reference Materials

If no official reference standard is available, the means of establishing the primary standard shall be described.

Details concerning the characterisation of the working standards used in the testing of the batches specified under 2.1.P.5.4 of this chapter to determine their contents and the respective purity tests shall be submitted. If applicable, reference may be made to 2.1.S.5 - reference standards or materials - of this chapter.

2.1. P.7 Container and Sealing System

The packaging for the investigational new drug used in the bioequivalence study shall be specified.

2.1. P.8 Stability

The available stability data, including those for the derivation of the usability deadline proposed for the bioequivalence study, shall be submitted in tabular form. They should comprise at least the results of examinations under conditions accelerating degradation and conditions of long-term storage.

2.1. A Annexes

2.1. A.2 Evaluation of the Risk of Contaminations.

A risk assessment must be made for all substances of human or animal origin. Documentary proof of the virus safety of the investigational new drug shall be submitted. Proof shall be submitted of the preclusion and monitoring of viral and non-viral foreign agents (viruses, bacteria, fungi, mycoplasms).

Proof of conformity with the TSE directive shall be furnished. Furthermore, the guideline on minimising the risk of transmitting animal spongiform encephalopathy agents via human or veterinary medicinal products (EMEA/410/01 Rev. shall apply. 2 – October 2003 resp. in the valid version[20])

Annex III / 3

Requirements for the Chemical Pharmaceutical and Biological Documentation for Approved, Modified Reference Compounds in Clinical Trials.

During the preparation of clinical trials, sponsors frequently modify approved medicinal products in order to use them as reference or comparative compound in blinded studies.

Since the marketing authorisation holder of the reference compound merely bears responsibility for the unmodified product in its packaging as envisaged and approved for circulation, it must be guaranteed that the quality of the product, under special consideration of biopharmaceutical characteristics, is not significantly influenced by the modifications made by the sponsor of the clinical trial.

2.1. P Investigational Medicinal Product (IMP)

2.1. P.1 Description and Composition of the IMP

The complete qualitative and quantitative composition of the IMP shall be specified. An exception to this are approved MPs that are merely re-packed in different packaging.

All substances shall be referenced with reference to a pharmacopoeia or an in-house monograph.

For an approved MP, it is sufficient to refer to its name and approval number, including a copy of the instructions for use or SmPC.

For radioactive medicinal products, additional information on the radioactivity per reference unit shall be furnished.

2.1. P.2 Pharmaceutical Development

The modifications carried out on the approved reference compound shall be briefly described in respect of their effects on the quality of the product. In particular, all parameters pertinent to the function, stability and efficacy of the medicinal product, e.g. in-vitro release of active substance and pH value, shall be named and their comparability with the unmodified compound shall be substantiated.

In the case of solid, oral pharmaceutical forms, comparative release profiles for the original and the modified reference compound are to be submitted in order to substantiate unchanged

biopharmaceutical characteristics (compare: Note for guidance on bioavailability and bioequivalence, Annex II, Dissolution Testing *for demonstrating similarity of dissolution profiles(CPMP/EWP/QWP/1401/98)).* In cases in which the equivalence cannot be demonstrated in-vitro, additional supporting clinical data are required.

2.1. P.3 Manufacturing

2.1. P.3.1 Manufacturer

The name and address of the companies involved in the manufacturing and testing shall be supplied. In the event that several manufacturers participate in the production of the trial compound, their respective fields of responsibility shall be clearly specified.

2.1. P.3.2 Batch Formula

The manufacturing formula (formulation) for the batch to be used in the clinical trial shall be specified. An exception to this are approved compounds that are merely re-packed in different packaging. For the approved compound itself, no further information is required.

2.1. P.3.3 Description of the Manufacturing Process and of the Process Control Procedures.

All stages of the modification process/preparation shall be described, including the in-process controls conducted (with specification of the limit values).

2.1. P.4 Control of the Auxiliary Substances

All auxiliary substances used in the modification of the reference compound shall be specified.

2.1. P.4.1 Specifications

If a monograph is available, reference shall be made to the Ph. Eur. or a pharmacopoeia of one of the EU member states. For auxiliary substances that are monographed neither in the above mentioned pharmacopoeia nor in the USP nor in the JP, the specifications must be listed and the pertinent analysis certificates shall be submitted.

2.1. P.4.2 Analytical Methods

If no reference can be made to one of the pharmacopoeia monographs listed under 2.1.P.4.1 of this chapter, the analytical methods used must be specified.

2.1. P.4.5 Auxiliary Substances of Human or Animal Origin

See in Annex III / 1, Annex 2.1.A.2.

2.1. P.5 Control of the Modified Reference Compound

2.1. P.5.1 Specification(s)

The specifications for the modified/prepared reference compound, including substantiated information concerning the respective analytic methods used, shall be submitted.

In general, the specifications shall comprise, apart from the description of the compound, the tests to determine the identity and contents of the active substance, of the impurities/degradation products and any other important pharmaceutical and technological characteristics (e.g. release characteristics).

2.1. P.5.2 Analytical Methods

The analytical methods used for the individual tests shall be specified. For test methods with clinical relevance used for specific pharmaceutical forms the methods shall be specified (e.g. methods for the determination of in-vitro release of the active substance).

2.1. P.5.3 Validation of the Analytical Methods

The suitability of the analytical methods shall be substantiated. The parameters of the respective test method in the framework of the validation in conformity with ICH shall be submitted in tabular form (e.g. the values for the determination limit, linearity). A complete validation report shall be kept available for presentation on request.

2.1. P.5.4 Batch Analysis

The results of the analysis certificate for one or more batches of the modified reference compound shall be submitted.

2.1. P.5.5 Characterisation of the Impurities

If the reference compound has undergone larger modifications by the sponsor and the originator compound is not known as being stable under normal conditions, it must be demonstrated that the impurities profile has not changed compared with the originator compound.

For stable reference compounds that have only been modified to a small extent (e.g. encapsulation of a tablet with auxiliary substances that were already used for the tablet), it is sufficient to submit a brief explanation as to why the impurities are not quantified.
This requirement does not apply in the case of compounds that have merely been re-packed in a different packaging.

2.1. P.7 Container and container seal system

The type of packaging, packaging material and package size must be specified. Descriptions and specifications must be provided if materials deviate from those used for the original compound and/or the approved medication respectively.

2.1. P.8 Stability

The sponsor of a clinical study must ensure that the modified/prepared reference compound is stable at least for the period of the clinical trial. The available stability data, including the derivation of suggested usability period for the clinical trials is to be provided in tabular form. Depending on the level of modification of the approved medication and the time period of the clinical study to be carried out, a minimum of stability data should be available for the modified/prepared reference compound before commencement of the respective clinical study in order to allow an estimate of the influence of the respective changes regarding product safety and stability.

Where necessary, to ensure the appropriate quality of the reference compound an accompanying stability study is to be carried out over the period of the clinical trial. In the case of only small modification to the reference compound, a justification of the specified usability period may be sufficient. The calibration time is to be determined for radioactive medicinal products, as the shelf life also results from the physical half-life of the radioactive isotope.

Appendix III / 4

Requirements for the Chemical-Pharmaceutical and Biological Documentation for Approved Unmodified Reference Medicinal Products in Clinical Trials

For all chemically defined MPs which are authorized in an EU or EEA member state, in one of the ICH regions or in one of the MRA states and which are to be used as reference in a clinical trial, only the proof of the marketing authorisation is to be provided with reference to the marketing authorisation holder and the approval number.

The required details regarding the analytical process for a reduced trial scope (e.g. identity testing) are to be provided. The analyses or trials required for the proof of quality in accordance with article 13 Para. 3 No. 3 of Directive 2001/20/EG can be fulfilled by providing evidence of the existence of a marketing authorisation (or an equivalent document, if applicable) in combination with an identity test.

The sponsor of a clinical study must ensure that the reference MP compound is stable at least for the period of the clinical trial. This can be carried out by specifying the respective expiry dates for the above mentioned approved reference MP.
For compounds that do not fulfil the above mentioned requirements, full documentation analogous to the requirements for documentation for the investigational medicinal product is to be provided.
For pharmaceuticals that are only approved in a third country and whose active substance is a biological product of human or animal origin or pharmaceuticals which contain the biological constituents of products of human or animal origin or whose manufacture requires such constituents, virus safety documents must be provided (see Appendix III / 1, Appendix 2.1.A.2).
.
For reference compounds which have no marketing authorisation in an EU or EEA member state, in one of the ICH regions or in one of the MRA states and which are particular pharmaceuticals in the terms of Guideline 2003/63/EG such as blood preparations, vaccines or pharmaceuticals made from plasma, and for all pharmaceuticals for new therapies in the terms of Guideline 2003/63/EG, contact should be made with the appropriate federal authorities before an application is made to clarify the scope of documents to be provided.

Appendix III / 5

Requirements for the chemical-pharmaceutical documentation for non-approved placebos

2.1. P Placebo

2.1. P.1 Description of the composition of the placebo

The complete qualitative and quantitative composition of the placebo is to be specified. A short description of the form of administration including specification of the function of individual excipients is to be provided.

2.1. P.2 Pharmaceutical development

Where applicable a description of masking methods for taste, appearance and smell in comparison to the investigational medicinal product is to be provided.

2.1. P.3 Manufacture

2.1. P.3.1 Manufacturer

The name and address of the concerns involved in manufacture and testing are to be provided. If several manufacturers are involved in the manufacture of the placebo, the respective responsibilities of each manufacturer are to be clearly presented.

2.1. P.3.2 Batch formula

The manufacturing formula (recipe) for the batch to be used in the clinical trial is to be provided. If applicable, the time within which the batch size can be varied is to be declared.

2.1. P.3.3 Description of the manufacturing process and process controls

A flow-chart is to be provided depicting the individual manufacturing steps and the application of the respective substances. In addition a short description of the manufacturing processes is to be appended.

2.1. P.3.4 Controls of critical manufacturing steps and intermediary products

Data is not required for placebos, with the exception of manufacturing processes for sterile pharmaceutical types.

2.1. P.3.5 Process validation and/or evaluation

Process validation data is not required for placebos. Exceptions are sterilisation procedures which are not standard procedures of the Ph. Eur., USP or JP. In this case, the critical manufacturing procedures as well as the validation of the manufacturing procedure are to be presented in a summarised manner and the test methods for in-process controls are to be specified.

2.1. P.4 Controls of excipients

2.1. P.4.1 Specifications

If a monograph is available, reference is to be taken to the Ph. Eur., the pharmacopoeia of an EU Member State, the USP or the JP. For excipients which are not monographed in any of the abovementioned pharmacopoeias, the specifications are to be listed and corresponding analysis certificates are to be appended.

2.1. P.4.2 Analytical procedure

If a pharmacopoeia monograph reference as listed under 2.1.P.4.1 in this chapter cannot be taken, the analytical methods applied are to be specified.

2.1. P.4.4 Justification of specifications

Selected specifications are to be justified for excipients which are not recorded in a monographic record as detailed under 2.1.P.4.1 of this chapter.

2.1. P.4.5 Human or animal sourced excipients

See Appendix III / 1, Appendix 2.1.A.2.

2.1. P.4.6 New excipients

Detailed information regarding the manufacturing procedure, characterisation and control as well as product safety is to be provided for new excipients. The details listed in the CTD structure under 2.1.S. are to be provided.

2.1. P.5 Investigational medicinal products control

2.1. P.5.1 Specifications

The selected specification, i.e. the release and retention period specifications are to be specified amongst the provision of test method information and corresponding acceptance criteria. The specifications should contain at least one test procedure which allows a clear distinction between placebo and investigational medicinal product.

2.1. P.5.2 Analytical procedures

The analytical procedures are to be specified for all test parameters contained in the specification.

2.1. P.7 Container and closure system

The container and closure system used for the placebo used in the clinical trial and where necessary the associated reconstitution solutions must be specified. Descriptions and specifications must be provided if materials are not described in the pharmacopoeia of an EU Member State, the USP or the JP.

2.1. P.8 Durability

The shelf life should cover the period of the clinical trial. It should be ensured that the physical characteristics of the placebo correspond to those of the investigational medicinal product for the entire period of the clinical study. Stability studies are only to be carried out in cases where there is cause for doubt regarding changes and/or contamination (e.g. microbiological purity for multiple doses and/or hardness or appearance). Otherwise, justification of the respective specified shelf life is sufficient.

Appendices to Section IV

Documentation of preclinical trials

Appendix IV / 1

1. Pharmacodynamics

1.1 Primary pharmacodynamics

Before first use in humans the effects of the active substance are to be tested and described as far as possible in the planned therapeutic application. The results should be presented in tabular form as well as supported by plots of dose-effect curves and time-effect curves. Comparisons to known compounds of the same class or of a comparable pharmacological mechanism (principle of effect)

are to be carried out where appropriate. Results for studies of primary pharmacodynamics which were carried out during clinical development are to be submitted. Comparative in-vitro- and in-vivo-studies of the expression of the therapeutic gene are to be carried out for gene transfer pharmaceuticals. In the case of autogenic somatic cells which are to be used as vaccinations against the body's antigens (e.g. tumour antigens), proofs of efficacy and data regarding primary pharmacodynamic effects such as the induction of immunity often cannot be achieved through animal models as the immunological principle of rejection in xenogenic models is not comparable with the autogenic situation. Thus, surrogate models should be established, e.g. cell therapeutics derived from animal tissue or from cells, which are then tested for efficacy and pharmacodynamics in the same species.
Human compounds for somatic cell therapeutics can lead to irrelevant results in animal models (e.g. regarding immunotoxicity). Where necessary, corresponding surrogate models should be applied instead.

1.2 Secondary pharmacodynamics

Tests of secondary pharmacodynamics should be carried out in suitable test systems. The results should, where necessary, be presented in tabular form for each tested organ system and where logical should also be presented and evaluated using dose-effect curves and time-effect curves.

1.3 Safety pharmacology

Before starting a clinical trial, safety pharmacology tests in accordance with the *Note for guidance on safety pharmacology studies for human pharmaceuticals (CPMP/ICH/539/00)* should be carried out. The effects on vital functions (cardiovascular system, central nervous system and respiratory system) are to be recorded using the tests referred to as the *core battery.*

Critical diagnoses in these, in other animal experimental or clinical studies may make additional safety pharmacology studies necessary. The relevant results of the safety pharmacology studies should be presented and evaluated in tabular form for each tested organ system.

1.4 Pharmacodynamic interactions

Preclinical studies of pharmacodynamic interactions, especially for identifying interactions with a potential co medication should be carried out as required in accordance with the *Note for guidance on the investigation of drug interactions (CPMP/EWP/560/95)* and *Investigation of chiral active substances (EudraLex 3CC29A)*. If the investigational medicinal product is an authorised MP which is to be tested in combination with other approved MP, the estimation of potential pharmacodynamic interactions can be carried out on the basis of the literature. If the investigational medicinal product is being tested for the first time in combination (as a fixed combination or together with other pharmaceuticals, including possible isomers), preclinical studies of pharmacodynamic interactions of the intended combination should be carried out.
(see also *Guideline on the non-clinical development of fixed combinations of medicinal products (CHMP/EMEA/CHMP/SWP/258498/2005, draft)*).

Appendix IV / 2

2. Pharmacokinetics

Animal studies of systemic exposure should be evaluated before starting clinical trials. Additional information regarding absorption, distribution, metabolism and excretion should be available *before the beginning* of phase II, in order to be able to compare the pharmacokinetics between animals and humans.

Preclinical trial of pharmacokinetics should be carried out in accordance with the *Note for pharmacokinetics and metabolic studies in the safety evaluation of new medicinal products in animals (EudraLex 3BS11A)* and, as far as applicable in accordance with the *Note for guidance on pharmacokinetics - Guidance for repeated dose tissue distribution studies (CPMP/ICH/385/95)*.
The lack of pharmacokinetic studies must be justified.

2.1 Bioanalytical method

The bioanalytical method used and its applicability (validation) regarding specificity, accuracy, precision (intra-/interday?) and limits of quantification (e.g. lower, upper, linearity?), where necessary taking into account species differences, should be described briefly.

2.2 Absorption/bioavailability

Experimental data in animals regarding absorption/bioavailability following single and repeated administration (if required) should be presented and evaluated in tabular form with a description of the animals used (species, strain, sex), the treatment (investigational medicinal products, application type, dose) and the results.

Relevant results from in-vitro tests should also be briefly presented and evaluated.

2.3 Distribution

The time-dependent distribution of the trial compound in various organs and corpuscular blood constituents as well as plasma protein binding should be tested and presented in tabular form.
For gene transfer pharmaceuticals, data should be provided for the distribution of the vector and data regarding the exclusion of germline transfer of the vector and the therapeutic gene.

2.4 Metabolism

Studies on metabolism - should also include the presystemic metabolism (gastrointestinal tract and first liver passage). A flow-chart presentation of the metabolism with details of the species would be desirable. The results on enzyme induction and/or inhibition respectively should be presented in tabular form and where logical also be presented graphically.
Classic studies for biotransformation are generally not necessary for biologically/biotechnologically produced pharmaceuticals *(Note for guidance on preclinical safety evaluation of biotechnology derived pharmaceuticals,* 4.2.3 Metabolism *(CPMP/ICH/302/95)).*

2.5 Excretion

The excretion of the trial compound /metabolites via the various excretory pathways (urine, feces, bile etc.) should be quantified, presented and evaluated in tabular form.
Classic studies for excretion are generally not necessary for biologically/biotechnologically produced pharmaceuticals *(CPMP/ICH/302/95, 4.2.3 Metabolism*).

2.6 Pharmacokinetic interactions

Preclinical studies on pharmacokinetics should be carried out in accordance with the *Note for guidance on the investigation of drug interactions* (*CPMP/EWP/560/95*), *Investigation of chiral active substances* (*EudraLex Vol. 3, 3CC29A)*.
If the investigational medicinal product is being combined with other pharmaceuticals in clinical studies, preclinical pharmacokinetic interaction studies are to be provided. Furthermore, the

interaction potential of possible required concomitant medications is to be evaluated. If the investigational medicinal product is an authorised MP which is to be tested in combination with other authorised MP, the estimation of the pharmacokinetic interactions potential can be carried out on the basis of the literature. In particular the clinical relevance and the necessity of clinical pharmacokinetic interaction studies are to be discussed.

Appendix IV / 3

3. Toxicology

The active substance administered in toxicity study should be representative for the requested clinical trials with regard to the quantitative and qualitative composition, including impurities. Further details about the specifications of the trial compound, such as purity, stability and specified impurities are required to be given at least for the 2 and/or 4 week toxicity studies respectively. Details on the specification of the trial compound used in further toxicity tests are required when the data is relevant for a comparative toxicological review.
For biological pharmaceuticals (vaccinations, monoclonal antibodies, sera, blood preparations etc.) biotechnologically produced pharmaceuticals (CPMP/ICH/302/95) and anti-tumour products (CPMP/SWP/997/96), a limited test programme for genotoxicity, carcinogenicity as well as reproduction and development toxicity is generally acceptable. If any of these tests have not been performed, this is to be justified briefly.

3.1 Single dose toxicity

The studies should be carried out on two mammalian species in accordance with the *Note for guidance on single dose toxicity (Notice to applicants)* and/or comparable guidelines/regulations which correspond to the current scientific level of knowledge. A dose escalation study can be accepted as an alternative to single-dose toxicity testing.

3.2 Repeated dose toxicity

Study for toxicity after repeated dose should be carried out in accordance with the *Note for guidance on repeated dose toxicity (CPMP/SWP/1042/99)*.
The treatment period is to be determined depending on the planned duration of the clinical trial as described in the *Note for guidance on non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals (CPMP/ICH/286/95)* and the *Note for guidance on duration of chronic toxicity testing in animals (rodent and non-rodent toxicity testing; CPMP/ICH/300/95)* or as summarised in the following Table 3:

Table 3: Length of toxicity studies depending on the clinical trial

Length of the clinical trial	**Minimal length of toxicity studies for repeated doses**			
	Phase I and II clinical trials		**Phase III clinical trials**	
	Rodent	**Non-rodent**	**Rodent**	**Non-rodent**
Single dose	**2 weeks**	**2 weeks**		
Up to 2 weeks	**2 weeks**	**2 weeks**	**1 month**	**1 month**
Up to 1 month	**1 month**	**1 month**	**3 months**	**3 months**
Up to 3 months	**3 months**	**3 months**	**6 months**	**3 months**

Up to 6 months	**6 months**	**6 months**		**3 months**
> 3 months			**6 months**	**6 months**
> 6 months	**6 months**	**6 months**		

Possible effects of the immunogenicity of the substance need to be taken into account in the test planning and study period for biologically/biotechnologically produced pharmaceuticals. The summarised results are to be provided, sorted by dose groups, in tabular form for all studies. Changes induced by the trial compound are to be specified in this case. For quantitative results (e.g. for clinical-chemical parameters) the distribution of individual values are to be specified using appropriate parameters. The discussion shall cover all target organs with the induced changes, changes to clinical-chemical parameters, the NOEL derivation and if different the NOAEL. For recovery studies, distinction is to be made between partial and complete reversibility of changes.

3.3 Genotoxicity

Genotoxity tests should be carried out in accordance with the *Note for guidance on genotoxicity: Guidance on specific aspects of regulatory genotoxicity tests for pharmaceuticals (CPMP/ICH/ 141/95),* and the *Note for guidance on genotoxicity: A standard battery for genotoxicity testing of pharmaceuticals (CPMP/ICH/174/95)*.

Depending on the phase of the clinical trial the following tests have to be carried out at the least

prior to Phase I:
• Gene mutation studies in bacteria
• In-vitro studies on the cytogenetic evaluation of chromosomal damage in mammalian cells or in-vitro mouse lymphoma tk assay,

prior to Phase II:
• In-vivo studies to identify chromosomal damage in haematopoietic cells in rodents.
• In the case of inconclusive and/or positive results additional tests may be required. The relevance of positive results is to be evaluated. If possible, the mechanism (e.g. effects under physiologically relevant conditions, endpoint specificity) and the dose dependency (possibility of deduction of a threshold value) are to be taken into account.

3.4 Carcinogenicity

Carcinogenicity studies are generally not required as a prerequisite for the carrying out of clinical trials, yet can be necessary if there are concerns in accordance with the *Note for guidance on the need for carcinogenicity studies of pharmaceuticals (CPMP/ICH/140/95)*.

3.5 Reproduction and development toxicity

The study for reproductive and developmental toxicity should be carried out in accordance with the *Note for guidance on specific reproductive toxicology: Detection of toxicity to reproduction for medicinal products (CPMP/ICH/386/95)* and the *Note for guidance on reproductive toxicology: Toxicity on male fertility (CPMP/ICH/136/95, modification).*
The reproductive and developmental toxicity studies required for the different phases of the clinical development are summarised in the following Table 4:

Table 4: Required studies on reproduction and fertility

	Required studies		
	Phase I	**Phase III**	**Approval**
Man	Statement on evaluation of male reproductive organs in toxicity studies after repeated dose (14 day)	**male fertility study**	
Woman not of childbearing potential*(sterilised or postmenopausal)*	Statement on evaluation of female reproductive organs in toxicity studies after repeated dose (14 day). Woman not of childbearing potential can be included in clinical trials without the carrying out of reproduction toxicity studies.		
Woman of childbearing potential	*(Species in accordance with CPMP/ICH/386/95)* Embryo-foetal development studies(2 species: rodent and non-rodent; preferably rat and rabbit)	Female fertility study (at least 1 species, preferably rat)	Prenatal and postnatal development studies (at least 1 species, preferably rat)
Woman of childbearing potential *(without a safe method of contraception)*	**Woman of childbearing potential** not using a safe method of contraception can only be included in clinical trials if all female reproductive toxicity studies have been completed.		
Pregnant Women	Additional data on human exposure are required for pregnant women.		

For the majority of investigational medicinal products, in accordance with *CPMP/ICH/386/95,* the 3-study design is adequate, which combines the following reproduction toxicity studies:

a) Fertility and early embryonic development, encompassing the period of time from before mating through to conception and from conception to implantation,
b) embryo-foetal development, encompassing the period of time from implantation to palate fusion through to the end of the pregnancy.
c) Prenatal and postnatal development, encompassing the period of time from implantation to the weaning of the young (including cessation of brood care behaviour) and the period of time from the weaning of the young to their sexual maturity.

The summarised results are to be provided, sorted by dose groups, in tabular form for all studies, respectively. The statistical methods applied are to be specified.
The discussion should address whether the trial compound belongs to a compound class with known reproductive toxicological characteristics *(class alert)*. The evaluation should include maternal toxicity, type of reproductive toxicity (singular and/or multiple effects in one and/or several species) dose-effect relationship and toxicokinetics.

3.6 Local tolerance

Before first use on humans, testing of local tolerance should be carried out and evaluated in accordance with the *Note for guidance on non-clinical local tolerance testing of medicinal products (CPMP/SWP/2145/00)*.

3.7 Phototoxicity

When evaluating possible phototoxic characteristics of the trial compound, the specifications of the *Note for guidance on photosafety testing (CPMP/SWP/398/01)* need to be followed. An absorption spectrum from 290 to 700nm is to be included for the trial compound and for topical applications, in addition for the excipients of the formulation compound. A test substance which absorbs light between 290 and 700nm and is topically applied or which reaches the skin or eyes through systemic exposure is to be considered potentially phototoxic.
When testing potentially phototoxic investigational medicinal products, sufficient measures must be taken during and, where necessary, after the study period to protect the trial subjects from UV exposure and, where applicable, also from visible light. If at any time the exposure of these persons to UV rays (or where applicable visible light) cannot be excluded, a statement on the *photosafety* of the substance is to be provided.

3.8 Other toxicity studies

Studies of antigenicity, immunotoxicity and mechanistic studies can be required depending on the investigational medicinal product. If such studies should be carried out, the respective guidelines should be followed.

Appendix IV / 4

4. Toxicity studies as prerequisite for clinical trials involving women and children

4.1 Women

The requirements for preclinical studies for clinical trials involving women are described in chapter 3.5. In exception to Table 4 in chapter 3.5, in justified exceptional cases, fertile women may be included in phase I/IIa without the data of preclinical studies on embryo-foetal development, if the clinical trial is investigating a life-threatening disease and the individuals involved are using highly effective contraception in accordance with Note 3 of the *Note for guidance on non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals (CPMP/ICH/286/95).*

4.2 Children

The preclinical study program should be largely completed for clinical trials planned to involve children. Carcinogenicity studies can be required before the beginning of clinical trials on children if long term treatment is planned. If data exists for the trial compound resulting from adult patients, this should be included in the evaluation. Toxicological trials on juvenile animals require a case by case decision (see also *Guideline on the need for non-clinical testing in juvenile animals on human pharmaceuticals for paediatric indications (EMEA/CHMP/SWP/169215/2005, draft)*).

Appendices to Section V

Appendix V / 1

Schematic overview of the specifications of characteristics of investigational medicinal product(s) expected normally before the commencement of clinical trials in phases I, II, III and IV in accordance with the recommendations of *Guideline CPMP/ICH/291/95*

Table 5: Clinical documentation required as prerequisite for the carrying out of clinical trials

Clinical documentation required as prerequisite for the carrying out of clinical trials

Phase I	***Phase II***	***Phase III***	***Phase IV***
Before commencement of first use in humans, the pharmaceutically active constituents in the investigational medicinal product must be tested regarding **Pharmacodynamics, Pharmacokinetics and Toxicity** to such a degree that the intended dosage range, type and period of use on humans, inclusion / exclusion criteria for test patients and where necessary the required medical safety measures as per the trial plan can be appropriately justified.	Before the beginning of clinical trials in phase II, the intended dosage range, dosage scheme and the type and period of use on humans, should be tested within the scope of phase I regarding **Pharmacodynamics, Pharmacokinetics and tolerance** to such a degree, and the results should be documented with appropriate data to such a degree, that the risks associated with its use can be estimated.	The dose range to be tested and the intended dosage scheme should be tested in phase I and phase II clinical trials to the degree corresponding to that detailed in the respective application, regarding **Pharmacodynamics, Pharmacokinetics, efficacy and tolerance** to such a degree, and the results should be documented with appropriate data to such a degree, that the risks associated with its use can be estimated.	As a rule the clinical trial of a pharmaceutical which is approved in an EU member state requires only the provision of appropriate scientific information and/or the S*ummary of product characteristics* (SmPC) selected by the sponsor, as long as the indication, administering form, type of application, and intended dosage range as foreseen in the trial plan correspond to the conditions of the scientific information provided and/or the SmPC.
For phase I clinical trials before which previous experience with the application of the investigational medicinal product on humans exists, this prior experience is to be documented and provided with the request for trial authorisation.	Furthermore, extensions of preclinical trials are required depending on the type of application, and period of application of the investigational medicinal product as well as trial subject / patient population included in testing.	Furthermore, extensions of preclinical trials are required depending on the type of application, and period of application of the investigational medicinal product as well as trial subject / patient population included in testing	In the case of deviation from the conditions of use in the scientific information provided and/or the SmPC, additional documentation may be required to be provided, depending on the type of deviation. The clinical trial must be allocated to another phase if necessary.

Appendix V / 2

2. Clinical documentation for the request for authorisation

Explanation of the specifications of the *Detailed guidance for request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial (ENTR/CT 1, Appendix 4, Common technical document headings for clinical data).*

2.1 Clinical pharmacodynamics

2.1.1 Brief summary

All pharmacodynamic clinical trials on healthy trial patients should be presented in tabular form in accordance with the specifications under Section V para. 1.2. The tabular presentation can be summarised in a combined table for clinical pharmacodynamics, clinical pharmacokinetics (see 2.2.1) as well as efficacy and tolerance (see 2.3.1). Reference to the details contained in the investigator's brochure (IB) is also possible.

2.1.2 Primary pharmacodynamics including the mechanism of primary effect

The results of clinical trials of the primary pharmacodynamics and, where necessary, the effect mechanism are to be presented as far as possible with regard to their dose-effect and time-effect relations.
If possible, they should be evaluated in comparison to known compounds of the same active substance group and/or a comparable pharmacodynamic effect principle with regard to selectivity, safety, effect strength, agonistic/antagonistic effects and for consistency or discrepancies compared to the results of the preclinical trial.
If active metabolites contribute to the primary effect in a relevant manner, the results should be presented analogously. The justification for the way herbal preparations were developed is to be presented based on the results of the pharmacodynamic tests of the preparations relevant to the request for authorisation. If an allocation is made to one of the extract types in the extract monographs of the Ph. Eur., this must be plausible on the basis of the documentation provided.

2.1.3 Secondary pharmacodynamic effects

Relevant results of clinical pharmacological studies should be presented and evaluated in tabular form. If appropriate, the results are also to be presented as far as possible with regard to their dose-effect and time-effect relations.
A critical analysis and evaluation of secondary pharmacodynamic effects should be carried out in view of the safety of individuals involved and where necessary in view of required special monitoring measures as well as the transferability of the results of preclinical trials for later application on humans.

2.1.4 Pharmacodynamic interactions

Clinical interactions studies of the pharmacodynamics may be required, depending on the accompanying medication expected on the basis of the planned clinical trials, the population included in the study and the results of the preclinical studies on pharmacodynamic interactions as well as with consideration of the characteristics of the investigational medicinal product (see *Note for guidance on the investigation of drug interactions (CPMP/EWP/560/95)*.

This type of study need not be carried out if no indications of pharmacodynamic interaction result from the preclinical studies and current scientific knowledge does not give rise to the expectation of such interactions. Results which are clinically relevant for the trial plan are to be presented, as far as possible, with quantitative information and with regard to the elucidated dose-effect or dose-frequency relations.

The results of the completed pharmacodynamic interaction studies and/or other data regarding pharmacodynamic interactions should be critically discussed and evaluated in particular with regard to the following aspects:

a) Relevance for the requested clinical trial due to:
   - the intended accompanying medicine,
   - the individuals to be involved in the trial,
b) Necessity of measures to be determined in the trial plan for monitoring the safety of individuals to be participating in the requested clinical trial.

2.2 Clinical pharmacokinetics

The clinical trials for pharmacokinetics should be carried out under consideration of the *Note for guidance on pharmacokinetic studies in man (EudraLex 3CC3A)*. In addition, for studies of plasma concentration-effect relations, of dose dependency as well as for the chronological sequence of

pharmacokinetics, the *Note for guidance on dose response information to support product authorisation (CPMP/ICH/378/95)* should be taken into consideration.

2.2.1 Brief summary

All clinical trials for pharmacokinetics on healthy test subjects and/or test patients should be presented in tabular form in accordance with the specifications in Section V para. 1.2.

2.2.2 Absorption

If appropriate, the degree of absorption and the speed of absorption and/or the bioavailability for the dose range intended for the requested clinical trials should be presented. The relevant pharmacokinetic parameters for absorption following single and where relevant multiple doses should be presented and evaluated in tabular form.

2.2.3 Distribution

Results for distribution of the active substance and its metabolites within the human organism (e.g. binding to blood cells and plasma proteins) should be presented and evaluated in tabular form for the dose range intended for the requested clinical trials.

In as far as they are relevant and available, the results of tests using imaging procedures should be briefly summarised and evaluated.

2.2.4 Elimination

2.2.4.1 Metabolism

In-vitro and in-vivo studies of metabolism of the active substance should - where available - be reported and the relevant results should be presented in tabular form:
Should results regarding the extent of any possible first pass metabolism and its effects on the bioavailability of the active substance be present for the dose range and type of application to be tested, these are to be presented.

2.2.4.2 Excretion

Where available, the excretion of the active substance and its metabolites as well as the different excretory pathways (urine, faeces etc) should be presented and evaluated in tabular form for the intended clinical trial dose range as a fraction of the applied dose.

2.2.5 Pharmacokinetics of active metabolites

The pharmacokinetics of active metabolites of the active substance should be presented and evaluated in tabular form in so far as they are of clinical relevance.

2.2.6 Plasma concentration-effect relations

If relevant data already exists from studies of the relationship between plasma concentration and pharmacodynamic effects, this data should be presented in tabular form and where necessary an evaluation of the described plasma concentration-effect relations in comparison to the conditions of use in the requested trials should be provided in consideration of the following aspects:
a) Dose range and dosage scheme,
b) Plasma concentrations,
c) Study population,
d) Pharmacodynamic effects and/or clinical end-points,

e) Deviations from results of analogous preclinical studies.

2.2.7 Dose dependency and course of pharmacokinetics over time

Results for the dose dependency and the course of pharmacokinetics of the active substance(s)of the investigational medicinal product should be presented in tabular and graphic form following single dose and also in *steady state* where applicable.
An evaluation of the results should be carried out in view of the requested trial's intended dosage, dosage schemes, type and period of use and the study population taking into account the following aspects:

a) Dose range,
b) Linearity,
c) Accumulation,
d) Time until *steady state* concentration is reached.

2.2.8 Pharmacokinetics of specific patient populations

Studies of the pharmacokinetics of specific patient populations (e.g. women, men, children, elderly patients, people with limited organ function, ethnic groups, special genetic characteristics) should be carried out under consideration of the relevant guidelines the *Note for guidance on studies in support of special populations: geriatrics (CPMP/ICH/379/95)* and *Note for guidance on clinical investigation of medicinal products in the paediatric population (CPMP/ICH/2711/99)*.

The results should be evaluated in relation to the plasma concentration-effect and where necessary toxicity relations for humans taking into account, where necessary, any existing results regarding such from preclinical studies. Possible consequences for the study population as well as the requested trial's intended dosage, dosage schemes, type and period of use are to be presented under consideration of points a) to d) as listed under 2.2.7.
As far as it is available and relevant, information from population related analyses of pharmacokinetics should be include in the evaluation.

2.2.9 Pharmacokinetic interactions

Clinical pharmacokinetic interaction studies may be necessary depending on the requested trial's intended concomitant medication, the study population to be included and the results of preclinical trial of pharmacokinetic interactions and in consideration of the pharmacokinetic characteristics of the investigational medicinal product.

As a rule, pharmacokinetic interaction studies need not be carried out if no indications of pharmacokinetic interactions result from the preclinical studies and current scientific knowledge does not give rise to the expectation of such interactions.

If they are however necessary, clinical studies of pharmacokinetic interactions should be carried out under consideration of the *Note for guidance on the investigation of drug interactions (CPMP/EWP/560/95).*

The results of all clinical trials of pharmacokinetic interactions for the investigational medicinal product should be provided. Clinically relevant results are to be presented with quantitative details.

Data should be critically discussed and evaluated in particular with regard to the following aspects:
a) Relevance for the requested clinical trials due to:

- the intended accompanying medicine,
- the individuals to be involved in the trial,

b) Necessity of measures to be determined in the trial plan for monitoring the safety of individuals to be participating in the requested clinical trial.

2.3 Overview of use on humans

2.3.1 Brief summary

All clinical trials on healthy test subjects and/or test patients regarding efficacy and safety should be presented in tabular form. The results for healthy test subjects should be presented separately to those for test patients.

2.3.2 Overview of safety and efficacy

The overview regarding safety and/or efficacy should be created under consideration of the information available regarding the investigational medicinal product at the time the request is lodged. If results regarding safety and/or efficacy from different clinical trials and/or applications other than clinical trial differ clearly from one another or contradict one another, this data should be critically discussed and evaluated.

2.3.2.1 Overview of safety

The overview of safety should be presented in tabular summarised form depending on the phase of the clinical trial as outlined in Section V - 1.1.1 and Section V - 1.1.2. For phase IV studies the provision of a tabular summary is not required as per Section V - 1.1.3.

A tabular overview of the common side-effects as well as the serious side-effects should be provided depending on the different dosages and the comparable medication and presented per *organ system* and statement of *preferred terms* using the MedDRA[21] terminology. Where necessary, reference can be made to the annual safety reports.

The evaluation of the data regarding safety should be carried out in comparison with the tested compared medication (incl. the placebo) and – where applicable and where sufficient data is available - under consideration of the following points:

a) Causality
b) Degree of severity,
c) Chronological sequence,
d) Reversibility,
e) Dose and Dosage scheme,
f) Duration of treatment,
g) Total dosage,
h) Demographics (age, gender etc),
i) Accompanying medication and/or accompanying illnesses,
j) Plasma concentrations,
k) Overdosing,
l) Tolerance development,
m) Withdrawal symptoms and rebound phenomena,
n) Genetic particularities.

2.3.2.2 Overview of efficacy

Relevant quantitative information regarding the efficacy of the investigational medicinal product (incl. tested comparison preparation) should, where applicable, be presented and evaluated stating the following points:

a) Dose dependency,
b) Effect strength,
c) Chronological sequence of effect,
d) Reversibility of effect,
e) Underlying mechanism,
f) Where necessary, dose and/or exposure level where effects appear, in relation to the animal experiment results,
g) Frequency rate of "responders“,
h) Validity of studied end-points (surrogate parameter),
i) Accompanying therapy,
j) Accompanying illnesses,
k) Specific study population,
l) Gender-specific differences,
m) Genetic particularities.

The evaluation of efficacy should be carried out in view of the requested trial’s intended dose, dosage schemes, and the individuals to be involved.

2.3.3 Experience to date regarding use on humans other than clinical trials

Experience to date regarding use of the investigational medicinal product on humans outside clinical trials should only be presented and evaluated if it contains additional insights regarding the efficacy, safety and other safety-related aspects relating to the results provided for the clinical trials. Scope, population and duration of use should be briefly described.