The 12th amendment to the German Drug Law was initiated to implement the Clinical Trial Directive 2001/20/EC among other issues such as 2000/38/EG (Pharmacovigilance Directive) and 2003/94/EG (GMP Directive). Additionally, there is an associated ordnance or Verordnung on Good Clinical Practice (GCP).

The pre-requisites for a clinical trial in Germany are defined in articles 40, 41, 42 and 42a of the German Drug Law (AMG, Arzneimittelgesetz) concerning the procedures for Ethics Committees (ECs), the approval by the federal superior authorities (ie, Bundesinstitut für Arzneimittel und Medizinprodukte [BfArM] or Paul Ehrlich Institut [PEI]), as well as withdrawal, repeal or cessation of an approval which has already been granted.

Article 40 lists all the general pre-requisites. Among other requirements, the sponsor or his representative has to be a legal person or institution within the EU or the EEA. Article 41 lists special pre-requisites such as those for trials in children.

According to Article 42, a sponsor must seek approval from an Ethics Committee and one of the federal superior authorities (ie, Bundesinstitut für Arzneimittel und Medizinprodukte [BfArM] or Paul Ehrlich Institut [PEI]), as well as withdrawal, repeal or cessation of an approval which has already been granted.

The study design is not adequate to prove the safety or efficacy of the investigational medication

If other requirements listed in Article 40 Para. 1, 3 Nr. 2 to 9, Para. 4 and Article 41 are not met.

### Federal Superior Authorities (FSAs)
Completeness of the application is to be checked by the FSAs within 10 days. The authorisation can be withdrawn, repealed and the trial stopped if facts arise which suggest that this is necessary. If considered necessary, the authorities will provide the competent ECs with information from other clinical trials in respect to the study medication while maintaining anonymity of patient data and confidentiality of sponsor trade secrets.

### Application (§7)
BfArM has issued its own GCP circulation (3. Bekanntmachung zur klinischen Prüfung von Arzneimitteln am Menschen) which contains detailed information concerning the size, structure and content of the documentation required that has to be supplied when seeking approval for a clinical study. This guidance also contains the forms for application, notification of later changes and end-of-study information. The forms are in the German language but are consistent with the respective EU guidance forms (ENTR/CT1 of April 2004). (see http://www.bfarm.de/de/Arzneimittel/klin_pr/form/eingangsbestaetigung.rtf).

The Sponsor must submit the application in writing to both the competent federal superior authority (ie, BfArM or PEI) and the competent Ethics Committee.

All attachments can be supplied in either German or English unless otherwise stated. Application forms and attachments should also be supplied in electronic form. It is possible, but not mandatory, to file both applications in parallel.

### Documentation required for CTA
(i) For both EC and FSA:
1. Copy of the confirmation letter re EudraCT-number
2. A signed cover letter in the German language with EudraCT-number; trial protocol number; title of the study; information on specialities, and reference list of cited information
3. A signed study protocol (by "Leiter der klinischen Prüfung" [principal investigator] and sponsor/representative of sponsor) with complete title, EudraCT-number, trial protocol number, version number and date
4. Name and contact details of the sponsor and representatives in other EU/EEA Member States
5. Name and contact details of investigator sites, laboratories, main investigator and/or "Leiter der klinischen Prüfung"
6. If investigator is NOT a physician, professional background of investigator and reasons why his/her position is justified
7. Information on all other investigators
8. Code/name and characteristics of the investigational medication
9. The objectives of the study
10. The number, age and sex of the patients/volunteers
11. Criteria for selection of the people involved and statistical considerations (inclusion/exclusion criteria)
12. Reasons for the apportionment between the sexes
13. Plans for post-study treatment and medical care after study termination.
14. Negative opinions of other ECs, non-approvals by other authorities.
15. A declaration that subjects who do not consent to circulation of data will not be included in the trial.

(ii) Additional data requested by ECs only:
1. Importance of the study
2. Predictable risks and disadvantages versus expected benefit
3. Justification for inclusion of particular subjects
4. Persons who may be dependent on the sponsor or investigator
5. The financing of the study
6. CVs of investigators and other proofs of qualification
7. Economic and other interests of investigators concerning study medication (potential conflict of interest)
8. Information on the suitability of the study site
9. Information and documents concerning informed consent
10. Details of research methods and deviations from usual practice
11. Methods to be used to avoid parallel participation of the subjects in other clinical studies (waiting period)
12. Documentation of the health status of healthy volunteers
13. Insurance acc. § 40 AMG, para. 1 No. 8, para. 3
14. Compensation for investigators and subjects
15. Declaration that data protection regulations will be observed
16. Contracts to be made between sponsor and study sites
17. Measures planned when interruption or termination ahead of schedule is necessary
18. List of ECs involved (in the case of a multi-centre study)
19. When the study protocol is provided in English, a summary of the important parts in the German language is required.

(iii) Additional documents requested by FSA:
1. IMPD and documentation
2. For xenogenic cell therapy; a declaration
3. When genetically modified organisms are involved; an assessment of environmental risk, risk for non-treated persons, observation plan for impact, measures to be taken for management and plans for cases of emergency
4. Name and contact details of the competent EC and other competent authorities in other Member States where the study will be performed

The Investigational Medicinal Product Dossier (IMPD) can be replaced by an approved SmPC when the study medication has a Marketing Approval and it is intended that the study medication will be used in accordance with the SmPC (“on-label”). Otherwise, additional data regarding quality, pharmacology, toxicology and results of further clinical studies must be presented.

If the approved medicinal product is used in a blinded study, additional data concerning quality should be provided. If the study medication is part of a clinical study already approved by BfArM or PEI, the sponsor may refer to the data already presented but should indicate all deviations. If the study medication is a placebo substance, only information concerning quality and manufacture is necessary.

CTA submission and review process

(i) Ethics Committees (ECs; art. 8 GCP promulgation)

In single centre clinical trials the application must be made to the competent EC of the investigator. In multi-centre trials, the application has to be submitted to the “EC in charge”, ie, the competent EC of the Principal Investigator. The ECs of all other investigators should receive a copy of the application as well as all documentation. The “EC in charge” has a coordinating function in the review of the application.

1. A letter of receipt must be issued within 10 days
2. Formal deficiencies should be corrected by the applicant within two weeks
3. The EC approval should be send to the sponsor and the superior authority within a maximum of 60 days but this should be:
   ■ 30 days if single centre study
   ■ 14 days if a Phase I study which is part of an already approved development programme

However, this is increased to:

■ 90 days for a study with somatic cell therapy or genetically modified organisms
■ 180 days when the EC needs additional expert opinions
4. The clock can only be stopped once to ask for further documents.

(ii) The federal superior authorities (art. 9 GCP prom.)

1. A letter of receipt will be issued within 10 days
2. Formal deficiencies should be corrected by the applicant within two weeks
3. Time limits for evaluation are:
   ■ 30 days in general (medicinal products acc. To art. 42 para. 2, phrase 7 No. 2 to 4 AMG)
   ■ 14 days for a Phase I study which is part of an already approved
development programme (but not when xenogenic somatic cell therapy or genetically modified organisms are involved)

- 90 days for a study with genetically modified organisms
- 180 days when the EC needs additional expert opinions
- There are no limits for studies with xenogenic cell therapy

4. When there are justified objections, the sponsor is allowed to make changes to the application ONCE (within a maximum time of 90 days). Fifteen days after receipt of the changes, a final approval or denial letter (with justification) will be issued (with a copy to the EC in charge).

**Inspections**

Routine inspection for control reasons are performed by the state authorities, but the federal superior authorities are also allowed to inspect study sites, manufacturing sites, laboratories, and other facilities of the sponsor. (acc. art 7 or 10 of GCP-promie, art. 22 para. 2 AMG). All inspections are in the name of the EU, authorities from other EU Member States may be asked for support (and vice versa). Re-inspections are possible when the EMEA requests this because there were indications of national differences in GCP compliance.

A GCP inspection follows a complex procedure and a pre-scheduled plan. An inspection report will be issued to the inspected site, the sponsor and the Federal Superior Authority (FSA) detailing all deficiencies detected, measures to be taken and all other relevant information for the EudraCT-data base. If the site is considered as unsuitable for the trial, this information will also be forwarded to the EC in charge. Upon request (with reasons) EMEA and other authorities of Member States will also be informed.

**Changes after approval (art 10)**

All changes which are of relevance concerning:

- patient safety
- interpretation of the scientific data
- study outcome
- study management
- quality or safety of the investigational medication
- risk assessment for GMOs

must be approved by both the EC and the FSA.

Approval is considered to be given if FSA does not object within 20 days. Proposed or requested modifications from FSA should be implemented within 35 days. ECs must approve or disapprove such changes within 20 days. Additional sites can only be included if the EC in charge gives approval (within 20 days).

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**Workflow for application and review***

*Also valid for amendments and addition of investigation sites*
The EC is responsible for informing the FSA of its decision.

Additional duties of the sponsor

1.  Adverse Reaction (AR) reporting (in all cases of ARs or SUSARs, individual subject data should be “anonymised”):
   - All ARs must be recorded and submitted to the FSA, ECs, other authorities in the EU and investigators upon request.
   - All suspected unexpected serious ARs (SUSARs) must be reported to the FSA, ECs, other authorities in the EU and investigators within 15 days.
   - All suspected unexpected serious ARs that lead to the death of a patient must be reported to the FSA, ECs, other authorities in the EU and investigators within seven days. Further information regarding additional measures undertaken with regard to SUSARs should be reported within a further eight days.
   - All facts which may lead to a reassessment of the risk-benefit must be reported to the FSA, ECs, other authorities in EU and investigators within 15 days. These include:
     - Single cases of known but serious ARs with unexpected outcome
     - Change of incidence of known but serious ARs with clinical relevance
     - Suspicion of an unexpected serious AR when the patient concerned has already finished the trial.
     - All other events that may influence the safety of the concerned subjects.
   - A summary safety report on subjects suspected of suffering serious ARs must be issued and distributed to the FSA, ECs, other authorities in the EU and investigators within 15 days. These include:

2.  All risks from GMO-manufactured products that may threaten the health of non-concerned people or the environment must be reported to the FSA.

3.  End of trial notification:
   - The conclusion of the trial must be reported within 90 days to the FSA, ECs and other authorities in the EU. A summary report with relevant results should be forwarded to ECs and the FSA within one year.
   - All data must be archived for 10 years.

Additional duties of the investigator

The investigator may delegate all or parts of these duties to the sponsor provided this is documented in writing.

1.  Notification of the competent (state) authority
   - According to art. § 67 AMG the investigator must report each clinical trial to his/her competent authority by providing the following documentation:
     - Investigator (name, contact details, profession)
     - FSA (name, date of approval, changes)
     - EC in charge (date of assessment, approval of changes)
     - EudraCT-number of study protocol
     - Sponsor (name, contact details, representatives)
     - LKP, ie, principal investigator (name, contact details).
     - Test laboratories and other institutions involved
     - Study protocol: title, code, objectives, therapeutic indication, type of study, design, special characteristics of study subjects
     - Planned timelines
     - Study medication: name, strength, form, active ingredients, route of administration
     - Special information, ie, whether the medication is a narcotic, a GMO, a general therapeutic, or a general diagnostic, or if radiation legislation is affected
     - Details of comparator products (number, form etc).
   - The end of study must be reported within 90 days and a stoppage/abortion within 145 days, with explanations.

2.  Notification of the sponsor
   - Each serious adverse event (AE) must be reported immediately (except those expected AEs which are exempted from reporting by the study protocol). Subsequently a written report with details must also be submitted. All other reports of relevance mentioned in the study protocol (unexpected clinical, diagnostic findings) must be provided. Additionally, in the case of the death of a subject, all necessary additional information must be sent to the EC and the FSA.

Parts of this information have been translated from the homepage of Dr Kori-Lindner, MD, member of the Board of DGPharMed, the German society for pharmaceutical medicine (see http://www.kori-lindner.de)