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Ordinance on the implementation of Good Clinical Practice in the conduct of clinical trials on medicinal products for use in humans (GCP Ordinance - GCP-V)*

of 9 August 2004

On the basis of §^{**} 12 para. 1b no. 2 and § 42 para. 3 of the Arzneimittelgesetz [AMG, German Medicines Act] in the version of the Notification of 11 December 1998 (BGBl. I p. 3586), with § 12 para. 1b no. 2 inserted by Article 1 no. 10 letter a of the Medicines Act of 30 July 2004 (BGBl. I p. 2031) and § 42 para. 3 reworded by Article 1 no. 28 of the Act of 30 July 2004 (BGBl. I p. 2031), the Federal Ministry of Health and Social Security in agreement with the Federal Ministry of Economics and Labour hereby orders:

**Chapter 1
General provisions**

**§ 1
Purpose of the Ordinance**

(1) This ordinance aims to guarantee compliance with Good Clinical Practice in the design, conduct and documentation of clinical trials in humans and reporting on such trials. It aims to ensure that the rights, safety and well-being of the trial subject are protected and that the results of the clinical trial are credible.

(2) In the case of clinical trials on medicinal products consisting of or containing a genetically modified organism or a combination of genetically modified organisms, this Ordinance shall also aim to protect the health of non-trial subjects and the environment within its scope.

*) This Ordinance serves to transpose:

- Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (OJEC No. L 121 p. 34),
- Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use (OJEU No. L 262 p. 22) and
- Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC (OJEC No. L 106 p. 1).

**) '§' = 'section'

§ 2 Scope

The Ordinance shall govern the duties, areas of responsibility and procedures with respect to the design, authorisation, conduct and monitoring of clinical trials in humans in accordance with § 4 para. 23 of the AMG including bioavailability and bioequivalence studies, and with respect to their documentation and the reporting on such clinical trials. It shall also govern the protection of the health of non-trial subjects and environmental requirements in the case of clinical trials of medicinal products consisting of or containing a genetically modified organism or a combination of genetically modified organisms.

§ 3 Definitions

(1) Multi-centre clinical trial means a clinical trial conducted according to a single protocol but at more than one site, and therefore by more than one investigator, in which the other trial sites may also be located in other Member States of the European Union or in countries which are not Member States of the European Union.

(2) Protocol means the description of the objectives, design, methodology, statistical considerations and organisation of a clinical trial. The term encompasses successive versions of the protocol and protocol amendments.

(2a) Trial subject means an individual who participates in a clinical trial as either a recipient of the investigational medicinal product or a member of a control group.

(2b) Informed consent means the decision, which must be written, dated and signed, to take part in a clinical trial, taken freely after being duly informed of its nature, significance, implications and risks and appropriately documented, by any person capable of giving consent or, where the person is not capable of giving consent, by his or her legal representative. If the person concerned is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases.

(2c) Ethics committee means an independent body consisting of healthcare professionals and non-medical members, whose responsibility it is to protect the rights, safety and well-being of subjects within the meaning of paragraph 2a and to provide public assurance of that protection, by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent.

(3) Investigational medicinal products mean pharmaceutical forms of active substances or placebos being tested or used as a reference in a clinical trial in humans, or to produce specific reactions in humans, including unauthorised products and authorised medicinal products used in the context of a clinical trial in humans but in an unauthorised pharmaceutical form or for an unauthorised indication, or to gain further information about the authorised form.

(4) Investigator's brochure means the compilation of the clinical and non-clinical data on the investigational medicinal products used in the clinical trial which are relevant to the clinical trial in humans.

(5) Inspection means the act by the competent authority or the National Competent Authority

(NCA) of conducting an official review of premises, documents, facilities, records, quality assurance arrangements, and any other resources that are deemed by the competent authority to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organisation's facilities, laboratories, manufacturing premises for investigational medicinal products, or at other establishments. It serves to verify compliance with the rules of Good Clinical Practice (GCP), Good Manufacturing Practice (GMP) or compliance with the information in the application.

(6) Adverse event means any untoward occurrence in a trial subject administered an investigational medicinal product and which does not necessarily have a causal relationship with this treatment.

(7) Adverse reaction means all untoward and unintended responses to an investigational medicinal product unrelated to the dose administered.

(8) Serious adverse event or serious adverse reaction means any untoward event or reaction that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or a congenital anomaly or birth defect.

(9) Unexpected adverse reaction means an adverse reaction, the nature or severity of which is not consistent with the available information concerning the investigational medicinal product.

(10) Blinding means the deliberate withholding of information on the identity of an investigational medicinal product in accordance with the instructions of the protocol.

(11) Unblinding means the disclosure of the identity of a blinded investigational medicinal product.

Chapter 2

Requirements concerning investigational medicinal products

§ 4

Manufacture and import

(1) The manufacture, release and import of investigational medicinal products shall be governed by the Betriebsverordnung für Pharmazeutische Unternehmer [Regulations for pharmaceutical entrepreneurs] of 8 March 1985 (BGBl. I p. 546) in the applicable version. The labelling of investigational medicinal products shall be subject to § 5.

(2) The sponsor shall ensure that the manufacture and testing of the investigational medicinal product complies with the directions of the dossier concerning the product submitted to the NCA in accordance with § 7 para. 4 no. 1 and the manufacturing companies and test laboratories are suitable for those activities and authorised to pursue them. In the case of the use of authorised medicinal products within the meaning of § 5 para. 8, the requirements shall be deemed to have been fulfilled if the sponsor carries out no further manufacturing procedures apart from labelling.

§ 5

Labelling of investigational medicinal products

(1) In the case of an investigational medicinal product, labelling shall be such as to ensure protection of trial subjects and traceability, to enable the identification of the product and trial, and to guarantee proper use of the investigational medicinal product.

(2) Apart from the cases in paragraphs 3 to 5 or in other justified cases, investigational medicinal products may be marketed only if the containers and, where used, the outer packaging, bear the following generally understandable information in German in clearly legible and indelible form:

1. Name or company and address of the sponsor and those of his contractor (CRO), where he is not the sponsor himself,
2. Telephone number of the sponsor and that of his contractor (CRO), where he is not the sponsor himself, unless the telephone numbers are listed in an accompanying document to be handed to the trial subject,
3. Name and strength of the investigational medicinal product,
4. Batch number with the abbreviation "Ch.-B." or trial code no.,
5. Pharmaceutical form,
6. Content by weight, volume or number,
7. Method of administration,
8. Dosage instructions with single or daily doses or reference to an accompanying document or the instructions of an investigator,
9. Shelf-life (expiry date with the indication "use by" or, if the nature of the investigational medicinal product allows, date of subsequent testing), stating the month and year,
10. Protocol code to identify the clinical trial, the trial site, the investigator and the sponsor, unless included in an accompanying document which may be handed to the trial subject,
11. EudraCT number issued by the European data-base, unless included in an accompanying document,
12. Identification code of the trial subject and, where necessary, specification of the sequence of administration, unless contained in an accompanying document which may be handed to the trial subject,
13. Note that the medicinal product is intended for clinical trial,
14. Storage instructions, where envisaged in the authorisation for the clinical trial,
15. Warning that the investigational medicinal product is to be kept out of the reach of children, where the product is intended to be handed to the trial subject,
16. Special precautions for the disposal of unused investigational medicinal products or other special precautions in order to avoid risks to the health of non-trial subjects and the environment, or instructions for the return of the product.

If the container and outer packaging are permanently connected, the labelling on the outer packaging is sufficient. The information in sentence 1 no. 3 may be omitted in the case of a blinded investigational medicinal product, or encoded in an appropriate manner.

(3) Where the container and outer packaging of the investigational medicinal product are to be kept together permanently and the outer packaging bears the information listed under Paragraph 2 sentence 1, the container must bear at least the information in accordance with Paragraph 2 sentence 1 nos. 1, 3, 4, 5, 6, 7, 10 and 12; the information in Paragraph 2 sentence 1 no. 7 may be omitted in the case of solid oral pharmaceutical forms. Paragraph 2 sentence 3 shall apply accordingly.

(4) Press-through packages shall be marked with the information in accordance with Paragraph 2 nos. 1, 3, 4, 7, 10 and 12; the information in Paragraph 2 sentence 1 no. 7 may be omitted in the case of solid oral pharmaceutical forms. Paragraph 2 sentence 3 shall apply accordingly.

(5) In the case of containers of not more than ten millilitres in volume and in the case of ampoules, the information in accordance with Paragraph 2 need appear only on the outer packaging, but the containers and ampoules must bear at least the information in accordance with Paragraph 2 sentence 1 nos. 1, 3, 4, 7, 10 and 12. Paragraph 2 sentence 3 shall apply accordingly.

(6) Information in accordance with Paragraph 2 which is also given in another language, must have the same content in both language versions. Additional information is permitted, provided it is connected with the use of the investigational medicinal product, is important in the interest of health education and does not contradict the information in accordance with Paragraph 2.

(7) If the use-by date is to be extended subsequently, an additional label shall be applied to the container and, where used, to the outer packaging, showing the new expiry date or date of subsequent testing together with the batch number. The label may cover the previous date, but it must not cover the existing batch number.

(8) In the case of investigational medicinal products which are medicinal products authorised by the NCA or for which the Commission of the European Communities or the Council of the European Union has issued a marketing authorisation in accordance with Article 3(1) or (2) of Regulation (EC) No. 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJEU No. L 136 p. 1), and which are intended for use in the clinical trial without additional manufacturing procedures, special labelling on the containers and outer packaging in accordance with paragraphs 2 to 7 may be omitted, insofar as the concept of the clinical trial allows. Information in accordance with Paragraph 1 may also be given in an accompanying document.

§ 6

Emergency unblinding and product recall

In the case of blinded investigational medicinal products, the sponsor shall implement an emergency unblinding procedure which permits immediate identification and, where necessary, immediate recall of the investigational medicinal product. The sponsor shall ensure that the procedure discloses the identity of the blinded product only in so far as is necessary.

Chapter 3

Authorisation by the Federal authority and assessment by the ethics committee

§ 7

Submission of Application

(1) The sponsor shall submit, in written form, an application for authorisation of the clinical trial to the Federal authority responsible for the investigational medicinal product to be tested, and an application for a positive assessment of the clinical trial to the competent ethics committee. The documents to be attached to the application may be in German or English, unless ruled otherwise in the following. Application and documents shall also be submitted on an electronic data carrier. In the case of multi-centre clinical trials taking place at more than one trial site within the scope of the AMG, every other ethics committee responsible for an investigator under *Land* law (participating ethics committee) shall receive a copy of the application and the documents at the same time. The ethics committee with competence under § 42 para. 1 sentence 2 of the AMG shall be in overall charge of the processing of the application.

(2) The applicant shall attach the following information and documents to the application to the competent ethics committee and the application to the competent Federal authority:

1. Copy of the confirmation letter for the EudraCT number of the protocol issued by the European database,
2. Covering letter in German, signed by the sponsor or his representative, stating the EudraCT number, sponsor's protocol code and title of the clinical trial, pointing out special features of the clinical trial and indicating where the relevant information can be found in the further documents,
3. Protocol signed by the principal investigator or by the supervisor of the clinical trial and by the sponsor or his representative, stating the full title and working title of the clinical trial, EudraCT number, sponsor's protocol code, version and date,
4. Name or company and address of the sponsor and, where applicable, of his representative established in the European Union or a Contracting State to the Agreement on the European Economic Area,
5. Names and addresses of the institutions associated with the clinical trial as trial sites or trial laboratories, and of the principal investigator and the supervisor of the clinical trial,
6. Specification of the professions of investigators who are not doctors, the scientific requirements of the profession in question and the experience of patient care necessary in order to practise it, and an explanation that the profession in question qualifies the person to conduct research in humans, and an explanation of the special features of the clinical trial which justify the investigator status of a member of the profession in question,
7. Investigator's brochure,
8. Name and description of the investigational medicinal product and its active ingredients,
9. Subject of the clinical trial and its objectives,
10. Number, age and sex of the trial subjects,
11. Explanation of the criteria for the selection of trial subjects and the underlying statistical considerations,
12. Reasons why the chosen sex distribution in the group of trial subjects is appropriate in order to identify possible sex-specific differences in the efficacy or safety of the investigational medicinal product being tested,
13. Plan for the further treatment and medical care of the trial subjects after the end of the clinical trial,
14. Reasoned statements of negative assessments by the competent ethics committees of other Member States of the European Union or of other Contracting States to the

Agreement on the European Economic Area and refusals of applications for authorisation by the competent authorities of other Member States of the European Union or of other Contracting States to the Agreement on the European Economic Area; if positive assessments by an ethics committee or authorisation by a competent authority are made subject to conditions, those conditions shall be indicated,

15. Confirmation that trial subjects have been informed of the forwarding of their data, under a pseudonym, in the context of the documentation and notification obligations under § 12 and § 13, to the recipients mentioned therein; this shall contain an explanation that trial subjects who do not consent to the forwarding of such data shall not be included in the clinical trial.

(3) The following shall also be submitted to the competent ethics committee:

1. Explanation of the importance of the clinical trial,
2. Assessment and evaluation of the foreseeable risks and disadvantages of the clinical trial compared with the expected benefits for the trial subjects and persons becoming ill in future,
3. Justification of the inclusion of persons under § 40 para. 4 and § 41 paras. 2 and 3 of the AMG in the clinical trial,
4. Explanation concerning inclusion of persons who may be dependent on the sponsor or investigator,
5. Information concerning the financing of the clinical trial,
6. Curricula vitae or other appropriate evidence of qualifications of investigators,
7. Information concerning possible financial and other interests of investigators in connection with the investigational medicinal products,
8. Information concerning the suitability of the trial site, especially concerning the adequacy of the existing resources and facilities and of the personnel available for the conduct of the clinical trial and concerning experience in the conduct of similar clinical trials,
9. Information and documents received by the trial subjects, in German, and an explanation of the procedure for informed consent,
10. Description of the intended investigation methods and any departures from the investigations which are usual in medical practice,
11. Description of the intended procedure to ensure that trial subjects are not taking part at the same time in any other clinical trials or research projects or are taking part in the clinical trial before the end of a necessary waiting period,
12. Description of the way in which the state of health of healthy trial subjects is to be documented,
13. Evidence of insurance cover under § 40 para. 1 sentence 3 no. 8 and para. 3 of the AMG,
14. Arrangements made with respect to the remuneration of investigators and payment of trial subjects,
15. Statement concerning compliance with data protection requirements,
16. All essential elements of the contracts envisaged between the sponsor and the trial site,
17. Criteria for the suspension or premature termination of the clinical trial,

18. In the case of multi-centre clinical trials taking place at more than one trial site within the scope of the AMG, a list of the names and addresses of the participating ethics committees,
19. A summary of the main content of the protocol in German, if the protocol is submitted in English in accordance with Paragraph 2 no. 3.

(4) The following shall also be submitted to the competent Federal authority:

1. The dossier concerning the investigational medicinal product, with the following content:
 - a) Documents concerning quality and manufacture,
 - b) Documents concerning the pharmacological/toxicological tests,
 - c) Intended labelling,
 - d) Manufacturing permit,
 - e) Import permit,
 - f) Documents concerning results of previous clinical trials and other clinical information which has come to light,
 - g) Summarising risk/benefit assessment
2. Evidence of insurance cover in accordance with § 40 para. 1 sentence 3 no. 8 and para. 3 of the AMG, where the investigational medical product is a xenogenic cell therapeutic;
3. In the case of investigational medicinal products which consist of or contain a genetically modified organism or a combination of genetically modified organisms, pursuant to Annex II to Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC (OJEC No. L 106 p. 1), an explanation and assessment of the risks to the health of non-trial subjects and the environment, and an explanation of the intended precautions and pursuant to Annex III of that Directive, information on the genetically modified organism, information on the conditions of the clinical trial and the environment which may receive the genetically modified organism, information on interactions between the genetically modified organism and the environment, an observation plan to establish the effects on the health of non-trial subjects and the environment, a description of the planned supervision measures and information on resulting residues and their treatment and on emergency plans. The sponsor may also refer to documents submitted by a third party in a previous procedure, unless it is confidential information;
4. Name and address of the competent ethics committee under § 42 para. 1 sentences 1 and 2 of the AMG and name and address of the competent authorities of other Member States of the European Union and other Contracting States to the Agreement on the European Economic Area in which the clinical trial is being conducted.

(5) Contrary to Paragraph 4 no. 1, the summary of product characteristics (SmPC) may be submitted instead of the dossier, where the investigational medicinal product is a medicinal product which is authorised in a Member State of the European Union or for which the Commission of the European Communities or the Council of the European Union has issued a marketing authorisation pursuant to Article 3(1) or (2) of Regulation (EC) No. 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJEU No. L 136 p. 1), and which is to be used in the clinical trial in accordance with the summary of product characteristics (SmPC). If the authorised medicinal product is to be used contrary to the summary of product characteristics (SmPC), and the departure is solely a departure from the authorised indication, no additional data concerning quality, the results of the pharmacological/toxicological tests or clinical results need be submitted as a rule; in the

case of other departures, depending on the nature of the departure, additional data concerning quality, the results of the pharmacological/toxicological tests or clinical results need be submitted only if the information contained in the summary of product characteristics (SmPC) is not sufficient for the conditions of use envisaged in the protocol. If the authorised medicinal product or its active ingredient is manufactured by a manufacturer other than that described in the summary of product characteristics (SmPC) or in accordance with a different procedure, additional data concerning quality shall be submitted depending on the nature of the changes. If necessary, further results concerning pharmacological/toxicological tests and additional clinical results shall also be submitted. If the authorised medicinal product is blinded, additional information concerning quality shall be submitted depending on the blinding measures carried out.

(6) If the investigational medicinal product is the subject of a clinical trial already authorised by the competent Federal authority, the sponsor may refer to the documents concerning the investigational medicinal product submitted in the context of the previous authorisation procedure. If the sponsor has further results concerning quality and manufacture, pharmacological/toxicological tests or clinical results, which are not part of the documents concerning the investigational medicinal product to which he is referring, the latter shall also be submitted.

(7) If the investigational medicinal product is a placebo, the content of the dossiers concerning the investigational medicinal product shall be confined to the information in accordance with Paragraph 4 no. 1 letter a.

§ 8

Assessment by the ethics committee

(1) The competent ethics committee under § 42 para. 1 sentences 1 or 2 of the AMG shall confirm receipt of the duly completed application to the sponsor within ten days, stating the date of receipt, or ask him to remedy the stated procedural deficiency within a period of 14 days, if documents concerning the application are missing with no reason being given, or the application is not in accordance with the rules for other reasons.

(2) Within the period of up to 60 days after receipt of the duly completed application which applies under § 42 para. 1 sentence 9 of the AMG, the competent ethics committee shall send the sponsor and the NCA its reasoned assessment. During consideration of the application with a view to a positive assessment, the competent ethics committee may request additional information from the sponsor once only. The period shall be suspended until receipt of the additional information. The suspension starts on the day on which the request was sent by the competent ethics committee.

(3) If the application concerns a clinical trial being conducted at a single trial site within the scope of the AMG, the period referred to in Paragraph 2 shall be reduced to a maximum of 30 days. If the clinical trial is a phase I clinical trial which, as part of the same development programme comprising several clinical trials, is based on a clinical trial in the same development programme which has received a positive assessment from the ethics committee, the period shall be reduced to 14 days. These reductions shall not apply in the case of clinical trials of the medicinal products referred to in Paragraph 4.

(4) In the case of clinical trials of somatic cell therapeutics and medicinal products which contain genetically modified organisms, the period referred to in Paragraph 2 shall be extended to 90 days; a further extension of the period to a total of 180 days shall take effect

if the competent ethics committee calls in experts or expert opinion in the course of preparing its assessment. For the clinical trial of gene transfer medicinal products, the period shall be a maximum of 180 days. There shall be no time limit for assessment in the case of trials of xenogenic cell therapeutics.

(5) Multi-centre clinical trials conducted at more than one trial site within the scope of the AMG shall be assessed by the ethics committee in overall charge, in collaboration with the participating ethics committees. The participating ethics committees shall verify the qualifications of the investigators and the suitability of the trial sites within their area of competence. Their assessment in this respect must be submitted to the ethics committee in overall charge within 30 days after receipt of the duly completed application.

§ 9

Authorisation by the competent Federal authority

(1) The NCA shall confirm receipt of the duly completed application to the sponsor within ten days, stating the date of receipt, or ask him to remedy the stated procedural deficiency within a period of 14 days, if documents concerning the application are missing with no reason being given, or the application is not in order for other reasons.

2) The examination of the duly completed application shall be concluded within the applicable period in accordance with § 42 para. 2 of the AMG. If the NCA sends the sponsor reasoned objections, the sponsor may amend the application accordingly, once only, within a period of up to 90 days after receipt. After receiving the amendment, the NCA shall send the sponsor the authorisation of the application in writing within 15 days or, stating its reasons, the definitive refusal of the application. The competent ethics committee shall receive a copy. In the case of the medicinal products referred to in § 42 para. 2 sentence 7 nos. 2 to 4 of the AMG, the period referred to in sentence 3 shall be 30 days. There shall be no time limit for authorisation in the case of trials of xenogenic cell therapeutics.

(3) If the application concerns a phase I clinical trial which, as part of the same development programme comprising several clinical trials, is based on a clinical trial in the same development programme which has been authorised by the competent Federal authority, the applicable period shall be reduced to 14 days, provided the application is based on the information in accordance with § 7 para. 4 no. 1 letters a and c of the application already authorised, with no alterations. This reduction shall not apply in the case of clinical trials of the medicinal products referred to in Paragraph 4.

(4) In the case of clinical trials of gene transfer medicinal products, somatic cell therapeutics or medicinal products which consist of or contain a genetically modified organism or a combination of genetically modified organisms, the period referred to in § 42 para. 8 sentence 8 phrase 1 of the AMG shall be extended to up to 90 days; a further extension of the period to a total of 180 days shall take effect if the NCA calls in experts or expert opinion in the course of preparing its decision. There shall be no time limit for authorisation in the case of trials of xenogenic cell therapeutics. In the case of investigational medicinal products which consist of or contain a genetically modified organism or a combination of genetically modified organisms, the NCA shall decide in collaboration with the Federal Ministry of Food, Agriculture and Consumer Protection; the authorisation of the clinical trial by the NCA shall comprise the authorisation of the release of those genetically modified organisms in the context of the clinical trial.

(5) In the course of preparing its decision, the NCA may verify the information contained in

the application in accordance with § 42 para. 2 sentences 1 and 2 of the AMG or amended in accordance with § 10 para. 1 at the trial site, the manufacturing facility of the investigational medicinal product, the laboratories participating in the trial, the sponsor's facilities or in other institutions. To this end, agents of the competent Federal authority, in collaboration with the competent authority, may enter commercial and business premises during normal working hours, inspect documents and, provided personal data are not involved, make copies or photocopies and request information.

§ 10

Subsequent amendments

(1) Amendments to a clinical trial authorised by the NCA or given a positive assessment by the competent ethics committee, which are liable

1. To affect the safety of trial subjects,
2. To influence the interpretation of the scientific documents on which the trial is based, or the scientific value of the study results,
3. To change the nature of the direction or conduct of the study significantly,
4. To impair the quality or safety of the investigational medicinal product, or
5. In the case of clinical trials on medicinal products which consist of or contain genetically modified organisms, to alter the risk assessment for the health of non-trial subjects and the environment,

may be made by the sponsor only if those amendments have received a positive assessment from the competent ethics committee, insofar as they relate to the information and documents under § 7 paras. 2 or 3, and if they have been authorised by the competent Federal authority, insofar as they relate to the information and documents under § 7 paras. 2 or 4. The positive assessment shall be applied for to the competent ethics committee, the authorisation shall be applied for to the competent Federal authority. The application shall be supported by reasons.

(2) The competent ethics committee shall send the sponsor and the NCA a decision on the duly completed application for a positive assessment of the amendments within 20 days of its receipt. In the case of multi-centre clinical trials conducted at more than one trial site within the scope of the AMG, the amendments shall be assessed by the ethics committee in overall charge, in collaboration with the concerned ethics committees. The participating ethics committees shall examine the qualifications of the investigators and the suitability of the trial sites within their area of competence. In the case of medicinal products which are somatic cell therapeutics or gene transfer medicinal products or medicinal products which contain genetically modified organisms, or whose active ingredient is a biological product of human or animal origin or contains biological components of human or animal origin or requires such components for its manufacture, the period shall be 35 days. There shall be no time limit for assessment in the case of xenogenic cell therapeutics.

(3) If the NCA does not send the sponsor any reasoned objections to the amendments within 20 days after receipt of the duly completed application for amendments, it shall be deemed to have been authorised. The NCA may ask the sponsor to alter his proposed amendments in accordance with their directions. In the case of medicinal products which are somatic cell therapeutics or gene transfer medicinal products, which contain genetically modified organisms, or whose active ingredient is a biological product of human or animal origin or contains biological components of human or animal origin or requires such components for its manufacture, the period shall be 35 days. There shall be no time limit for authorisation in the case of xenogenic cell therapeutics.

(4) The sponsor may include additional trial sites within the scope of the AMG in the clinical trial only if the competent ethics committee which has given a positive assessment to the clinical trial gives a positive assessment to the inclusion of the relevant additional trial site. The information in accordance with § 7 para. 2 no. 5 and 8, para. 3 nos. 4, 6 to 8, 13, 14, 16 and 18 relating to the additional trial sites shall be attached to the application for a positive assessment. Every ethics committee which is responsible under *Land* law for an investigator who is responsible for the conduct of the clinical trial at an additional trial site shall receive a copy of the original application and the documents for a positive assessment of the clinical trial, the positive assessment of the ethics committee referred to in sentence 1 and the application for a positive assessment of the inclusion of the additional trial sites. The ethics committee in overall charge shall contact that ethics committee. The positive assessment shall be deemed to have been granted if the ethics committee in overall charge does not send the sponsor a reasoned reservation within 30 days of receipt of the properly completed application. The ethics committee in overall charge shall notify the NCA of the assessment.

§ 11

Measures to protect against immediate risk

(1) Notwithstanding § 10, the sponsor and the investigator shall immediately take all necessary measures to protect trial subjects against immediate risk, if new circumstances may affect the safety of trial subjects.

(2) In the case of clinical trials of medicinal products which consist of or contain a genetically modified organism or a combination of genetically modified organisms, the sponsor and the investigator shall take all necessary measures, notwithstanding § 10, to protect the health of non-trial subjects and the environment.

Chapter 4

Documentation and notification obligations, databases, inspections

§ 12

Notification, documentation and information obligations of the investigator

(1) The investigator shall attach the following information to his notification in accordance with § 67 of the AMG to the competent authority, for each clinical trial conducted by him:

1. Name, address and profession of the investigator subject to the notification obligation,
2. Name of the NCA and date of grant of authorisation and, where applicable, dates of authorisations of subsequent amendments in accordance with § 10 para. 1,
3. Name and address of the competent ethics committee under § 42 para. 1 sentences 1 or 2 of the AMG, and date of its positive assessment and, where applicable, dates of authorisations of subsequent amendments in accordance with § 10 para. 1,
4. Name and address of the participating ethics committee responsible for the investigator and the trial site and date of its relevant assessment,
5. EudraCT number of the protocol,
6. Name or company and address of the sponsor and, where applicable, of his representative established in the European Union or in a Contracting State to the Agreement on the European Economic Area,
7. Name and address of the supervisor of the clinical trial and of the principal investigator,
8. Name and address of the trial laboratories and other institutions involved by the

- investigator,
9. Full title of the protocol including protocol code and objectives,
 10. Indication to be investigated,
 11. Nature of the clinical trial and its conduct, including information on the special characteristics of trial subjects to whom the special conditions under § 41 of the AMG apply,
 12. Intended start and expected duration,
 13. Name, strength, pharmaceutical form, active substances and method of administration of the investigational medicinal product,
 14. Information on whether provisions of the laws on narcotics, genetic engineering or radiation protection are to be taken into consideration or whether the product involved is a somatic gene therapeutic or gene diagnostic,
 15. Number and nature of the reference products involved.

(2) The investigator shall notify the competent authority within 90 days of the end of the clinical trial. If the clinical trial was terminated or suspended by the sponsor, the notification shall be sent within 15 days, stating the reasons for the termination or suspension.

(3) The investigator may transfer the obligation to notify the competent authority to the sponsor, and shall document this.

(4) The investigator shall inform the sponsor immediately of the occurrence of a serious adverse event, with the exception of events which need not be reported immediately according to the protocol or investigator's brochure, and subsequently send him a detailed written report. Personal data shall be pseudonymized before they are sent, using the identification code of the trial subject.

(5) The investigator shall inform the sponsor of unexpected events and unexpected clinical/diagnostic findings described in the protocol as crucial for the assessment of the clinical trial, within the periods indicated in the protocol. Paragraph 1 sentence 2 shall apply accordingly.

(6) In the case of the death of a trial subject, the investigator shall provide to the competent ethics committee, in the case of multi-centre studies also to the participating ethics committee, to the NCA and to the sponsor, all additional information necessary for the fulfilment of their duties. Personal data shall be pseudonymized before they are sent, using the identification code of the trial subject.

(7) In the case of clinical trials of medicinal products which consist of or contain a genetically modified organism or a combination of genetically modified organisms, the investigator shall inform the sponsor immediately of any observed harmful effects on the health of non-trial subjects and the environment which were not envisaged in the risk assessment.

§ 13

Documentation and notification obligations of the sponsor

(1) The sponsor shall document in detail all adverse events notified to him by the investigators. The records shall be sent on request to the NCA and the competent authorities of other Member States of the European Union and other Contracting States to the Agreement on the European Economic Area in whose territory the clinical trial is being conducted. Personal data shall be pseudonymized before they are sent, using the identification code of the trial subject.

(2) The sponsor shall report every suspected case of an unexpected serious adverse reaction which has come to his attention immediately, but at the latest within 15 days after it comes to his attention, to the competent ethics committee, the NCA and the competent authorities of other Member States of the European Union and other Contracting States to the Agreement on the European Economic Area in whose territory the clinical trial is being conducted, and to the investigators participating in the clinical trial. Personal data shall be pseudonymized before they are sent, using the identification code of the trial subject.

(3) In every suspected case of an unexpected serious adverse reaction which has resulted in death or is life-threatening which has come to his attention the sponsor shall provide immediately, but at the latest within seven days after it comes to his attention, to the competent ethics committee, to the NCA and the competent authorities of other Member States of the European Union and other Contracting States to the Agreement on the European Economic Area in whose territory the clinical trial is being conducted and to the investigators participating in the clinical trial, all information which is important for the assessment and send them the further relevant information within eight further days. Personal data shall be pseudonymized before they are sent, using the identification code of the trial subject.

(4) The sponsor shall inform immediately, but at the latest within 15 days after it comes to his attention, the competent Federal authority, the competent ethics committee and the competent authorities of other Member States of the European Union and other Contracting States to the Agreement on the European Economic Area in whose territory the clinical trial is being conducted, of all circumstances which require a review of the risk/benefit assessment of the investigational medicinal product. Such circumstances shall include, in particular:

1. Case reports of expected serious adverse reactions with an unexpected outcome,
2. An increase in the frequency of expected serious adverse reactions which is assessed as clinically relevant,
3. Suspected cases of serious unexpected adverse reactions occurring after the trial subject has already completed the clinical trial,
4. Events in connection with the conduct of the study or the development of the investigational medicinal product which may affect the safety of the trial subjects.

(5) Where measures in accordance with § 11 are taken, the sponsor shall immediately inform the competent Federal authority, the competent authority, the competent ethics committee and the competent authorities of other Member States of the European Union and other Contracting States to the Agreement on the European Economic Area in whose territory the clinical trial is being conducted, of these measures and of the circumstances giving rise to them.

(6) Once a year during the trial, or on request, the sponsor shall submit to the competent ethics committee, the NCA and the competent authorities of other Member States of the European Union and other Contracting States to the Agreement on the European Economic Area in whose territory the clinical trial is being conducted, a list of all suspected cases of serious adverse reactions occurring during the trial, as well as a report on the safety of the trial subjects.

(7) If the sponsor receives, in the case of clinical trials of medicinal products which consist of or contain a genetically modified organism or a combination of genetically modified

organisms, new information about risks to the health of non-trial subjects and the environment, he shall report these immediately to the competent Federal authority.

(8) The sponsor shall notify the competent authority, the competent Federal authority, the competent ethics committee and the competent authorities of other Member States of the European Union and other Contracting States to the Agreement on the European Economic Area in whose territory the clinical trial is being conducted, of the end of the clinical trial within 90 days. If the clinical trial was terminated or suspended by the sponsor, notification shall be sent within 15 days, stating the reasons for the termination or suspension.

(9) Within a year after the end of the clinical trial, the sponsor shall send the NCA and the competent ethics committee a summary of the report on the clinical trial, covering all important results of the clinical trial.

(10) The sponsor shall ensure that the important documents of the clinical trial, including the protocol, are kept for at least ten years after the end or termination of the trial. Other provisions concerning the keeping of medical documents shall remain unaffected.

§ 14

Information obligations of the National Competent Authority

(1) The NCA shall inform the authorities responsible for supervision, the competent ethics committee and the Commission of the European Communities immediately, stating its reasons, of the ordering of remedial measures under § 42a para. 5 of the AMG.

(2) The NCA shall send the authority responsible for supervision all of the necessary documents on request.

(3) The NCA shall send information to the European database (EudraCT database) for clinical trials established within the European Medicines Agency, especially

1. Information on the application for authorisation of the clinical trial by the competent Federal authority,
2. Information on the application for a positive assessment of the clinical trial by the competent ethics committee,
3. Amendments to the application for authorisation of the clinical trial under § 9 para. 2 sentence 2,
4. Subsequent amendments under § 10,
5. End of the clinical trial,
6. Information on inspections carried out in order to verify compliance with Good Clinical Practice.

Personal data shall not be sent.

(4) At the request of the competent authorities of other Member States of the European Union and other Contracting States to the Agreement on the European Economic Area, of the European Medicines Agency or the European Commission, the NCA shall send the information in accordance with Paragraph 3 which has not yet been entered into the EudraCT database. Personal data shall not be sent.

(5) The NCA shall immediately send information on all suspected cases of unexpected

serious adverse reactions to an investigational medicinal product to the EudraVigilance database established within the European Medicines Agency.

§ 15 Inspections

(1) Inspections in the context of the supervision of ongoing or completed clinical trials shall be carried out by the competent authority in accordance with § 64 para. 1 of the AMG. Inspections to verify compliance with the information in the documents under § 7 or § 10 or with the documents under § 22 para. 2 no. 3 of the AMG shall be carried out by the competent Federal authority.

(2) Inspections shall be carried out on behalf of the European Community. Their results shall be recognised by the other Member States of the European Union. The competent authority or Federal authority may ask the competent authorities of other Member States for assistance in conducting inspections and shall assist in return in inspections initiated by those authorities. Paragraph 1 shall apply accordingly.

(3) Subject to the agreements made between the European Union and third countries, the NCA may submit a reasoned application to the European Commission requesting an inspection of the trial site, the sponsor's facilities or the manufacturer's facilities in a third country. If the inspection concerns a medicinal product for which an application for authorisation has been submitted to the competent Federal authority, the latter may carry out the inspection in the third country under its own responsibility.

(4) If the inspection concerns a medicinal product for which an application for authorisation has been submitted in accordance with the procedures in Regulation (EC) No. 726/2004 of the European Parliament and the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJEU No. L 136 p. 1), it shall be subject to coordination by the European Medicines Agency; it shall be carried out by the NCA taking into account the procedures laid down by the European Medicines Agency.

(5) A further inspection shall be carried out if it is required by the European Commission at the request of another Member State concerned by the clinical trial or the European Medicines Agency on the ground that discrepancies have emerged between the individual Member States of the European Union in the supervision of compliance with Good Clinical Practice.

(6) The inspection carried out by the competent authority shall be conducted in accordance with a written procedure and a pre-determined plan.

(7) An inspection report shall be prepared promptly, which shall include all important findings of the inspection, especially deficiencies and complaints. In the case of an inspection under § 64 para. 1 of the AMG, the inspection report shall also include orders to remedy the deficiencies and complaints found. The inspection report drawn up by the competent authority shall be sent to the inspected institution and the sponsor with the request to remedy the deficiencies and complaints, and the protection of confidential information shall be guaranteed. The competent authority shall send the NCA the information on inspections carried out which is required to be transmitted to the EudraCT database under § 14 para. 3 no. 6. If the inspection reveals that the investigator responsible for the conduct of the clinical trial at a trial site or the trial site are not suitable, the inspection report shall be made

available to the ethics committee responsible for the investigator and, in the case of multi-centre clinical trials, to the ethics committee in overall charge. On a reasoned request, the inspection report shall also be made available to the European Medicines Agency and the competent authorities of other Member States of the European Union. The assessment of the reply sent by the sponsor concerning the remedying of deficiencies and complaints shall be the responsibility of the competent authority in accordance with a specified procedure.

(8) In the event of imminent danger, the competent authority shall order the immediate suspension of the trial and notify that suspension immediately to the sponsor and the competent Federal authority. The NCA shall consider the introduction of measures in accordance with § 42a of the AMG and inform the competent authorities of the measures which it has taken. The competent authority may, if necessary, adopt further measures under § 69 of the AMG on its own responsibility.

(9) The competent authority and the NCA shall have a carefully designed and correctly managed quality assurance system which comprises at least the organisation structures, responsibilities and procedures. The quality assurance system shall be fully documented and its ability to fulfil its functions shall be monitored. The personnel responsible for carrying out the inspections shall be present in sufficient numbers and shall be qualified for their duties as well as independent and free from commercial, financial or other constraints which may affect their decision. The persons responsible for supervision shall be given the opportunity to participate regularly in specialist training courses. The qualifications of the personnel shall be verified.

Chapter 5 Transitional and final provisions

§ 16 Infringements

Whosoever, intentionally or negligently

1. Fails to make a report, or to make it correctly, completely or in time, contrary to § 12 para. 4 sentence 1 or para. 7 or § 13,
2. Fails to send information, or to send it correctly, completely or in time, contrary to § 13 para. 3 sentence 1,
3. Fails to submit a list or report, or to submit them correctly, completely or in time, contrary to § 13 para. 6, or
4. Fails to make a notification, or to make it correctly, completely or in time, contrary to § 13 para. 7, commits an infringement within the meaning of § 97 para. 2 no. 31 of the AMG.

§ 17 Transitional provisions

Clinical trials of medicinal products for which the documents required under § 40 para. 1 sentence 2 of the AMG in the version applicable until 6 August 2004 have been submitted before 6 August 2004 to the ethics committee responsible for supervisor of the clinical trial,

shall not be subject to the provisions of this Ordinance.

§ 18
Entry into force

This Ordinance shall enter into force on the second day after its promulgation.

The Bundesrat [Federal Upper House of Parliament] has given its consent.

Bonn, 9 August 2004

The Federal Minister for Health and Social Security
pp.
K. T. Schröder

This is an unofficial English translation of the German ordinance „*Verordnung über die Anwendung der Guten Klinischen Praxis bei der Durchführung von klinischen Prüfungen mit Arzneimitteln zur Anwendung am Menschen (GCP-Verordnung –GCP-V)* as published in the Federal Law Gazette on 12 August 2004 (*Bundesgesetzblatt Jahrgang 2004 Teil I Nr. 42, ausgegeben zu Bonn am 12. August 2004*).

The German original is the binding version in any case of doubt or discrepancy.

If you notice any inconsistency in this translation, please send your comments to clintrials@bfarm.de

Abbreviations:

AMG	Arzneimittelgesetz	German Medicinal Products Act
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte	Federal Institute for Drugs and Medical Devices
BGBl	Bundesgesetzblatt	Federal Law Gazette
EudraCT	Europäische Datenbank für klinische Prüfungen	European Clinical Trials Database
NCA	zuständige Bundesoberbehörde	National Competent Authority
PEI	Paul-Ehrlich-Institut Bundesamt für Sera und Impfstoffe	Paul-Ehrlich-Institute Federal Agency for Sera and Vaccines
SmPC	Zusammenfassung der Merkmale des Arzneimittels	Summary of product characteristics
ZLG	Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten	Central authority of the Laender for Health Protection Regarding Medicinal Products and Medical Devices

Comments:

Germany has two *Bundesoberbehörden* (National Competent Authorities; NCA) that share the responsibilities for medicines for human use:

1. **Paul-Ehrlich-Institut**, responsible for the granting of marketing authorization, inspection and the permission of clinical trials of (immuno-) biological drugs for human and veterinary use. According to § 77 of the AMG, these products include sera, vaccines, blood preparations, test allergens, test sera and test antigens (for details, see www.pei.de)

2. **Bundesinstitut für Arzneimittel und Medizinprodukte**, responsible for the granting of marketing authorization of medicinal products, the post-marketing surveillance of medical devices and the permission of clinical trials for all other medicines (for details, see www.bfarm.de).

The responsibilities for inspection and supervision of manufacturing, marketing and post-marketing surveillance are divided between the NCAs and the competent authorities of the Länder. The coordination between the competent authorities of the Länder is organized by the **Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten** (for details, see www.ZLG.de)