Implementation of Directive 2001/20/EC on GCP and Clinical Trials in Germany

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Federal Institut for Drugs and Medical Devices (BfArM), Bonn
**Commission Directive .../... / EC**

laying down principles and guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of manufacturing or importation of such products

summarizes

**Detailed Guidelines (2001/20/EG Art. 1)**
on the principles of good clinical practice in the conduct in the EU of clinical trials on medicinal products for human use

**Detailed Guidelines (2001/20/EG Art. 13)**
on the community basic format and the contents of the application for a manufacturing and/or importation of an investigational medicinal product for human use

**Detailed Guidelines (2001/20/EG Art. 15)**
on inspection procedures for verification on GCP compliance

**Detailed Guidelines (2001/20/EG Art 15)**
on the qualifications of inspectors who should verify compliance in clinical trials with the provision of good clinical practice for an investigational medicinal product

**Detailed Guidelines (2001/20/EG Art. 15)**
on the trial master file and archiving
Directive 2001/20/EG Article 13

- Art. 13 2001/20/EC implements GMP for IMPs
- Annex 13 of the directive 91/356/EEC is binding for IMPs
<table>
<thead>
<tr>
<th>Phasen der klinischen Prüfung</th>
<th>Prüfpräparate, die Wirkstoffe enthalten, zu denen es in D bereits zugelassene AM gibt</th>
<th>Prüfpräparate, die Wirkstoffe enthalten, zu denen es in D keine zugelassenen AM gibt</th>
<th>Summen</th>
</tr>
</thead>
<tbody>
<tr>
<td>in Phase I</td>
<td>222</td>
<td>222 / 14%</td>
<td>444 / 28%</td>
</tr>
<tr>
<td>in Phase II</td>
<td>176</td>
<td>159 / 10%</td>
<td>335 / 21%</td>
</tr>
<tr>
<td>in Phase III</td>
<td>297</td>
<td>123 / 8%</td>
<td>420 / 26%</td>
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<tr>
<td>Zwischensumme Anzahl Prüfpläne</td>
<td>695</td>
<td>504</td>
<td>1199 / 75%</td>
</tr>
<tr>
<td>in Phase IV Schätzung</td>
<td>401</td>
<td>/</td>
<td>401 / 25%</td>
</tr>
<tr>
<td>Summen / %</td>
<td>1096 / 68%</td>
<td>504 / 32%</td>
<td>1600 / 100%</td>
</tr>
</tbody>
</table>
Implementation in Germany

- **12th Revision of the German Drug Law (AMG)**
  - (ratification by German parliament and the `Bundesrat´ will be expected in the mid of 2004 !)

- **Ordinance performing clinical trials on human medicinal products**
  (Ministry of Health and Social Protection)
  - first draft, dated 2nd September 2003
  - Announcement of the BfArM /PEI and German ECs
  - first draft will be published for discussion ([http://www.bfarm.de](http://www.bfarm.de))
Legal Levels

European Level

Directive 2001/20/EC
´… conduct of Clinical Trials´
Commission Directive
´Principles and Guidelines for GCP´

German Level

12. Revision AMG
Ordinance acc. to § 42 AMG

Detailed Guidances

1a

Announcement BfArM/PEI/ECs
Detailed Guidances

2a
<table>
<thead>
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<th></th>
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<tr>
<td>1</td>
<td>§ 40</td>
<td>§§ 1, 2</td>
<td>Scope</td>
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<td>2</td>
<td>§ 4</td>
<td>§ 3</td>
<td>Definitions</td>
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<td>3</td>
<td>§ 41</td>
<td></td>
<td>Protection of clinical trial subjects</td>
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<td>4</td>
<td>§41, 2</td>
<td></td>
<td>Clinical trials on minors</td>
</tr>
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<td>5</td>
<td>§41, 3</td>
<td></td>
<td>Clinical trials on incapacitated adults</td>
</tr>
<tr>
<td>6, 7, 8</td>
<td>§ 42,1</td>
<td>§§ 6, 7</td>
<td>Ethics-Committee + single opinion</td>
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<tr>
<td>9</td>
<td>§ 42,2</td>
<td>§ 8</td>
<td>Commencement of a clinical trial</td>
</tr>
<tr>
<td>10</td>
<td>§ 9, 11</td>
<td></td>
<td>Conduct of a clinical trial (including end of trial)</td>
</tr>
<tr>
<td>11</td>
<td>§ 15, 16</td>
<td></td>
<td>Exchange of information</td>
</tr>
<tr>
<td>12</td>
<td>§42a</td>
<td>§ 10</td>
<td>Suspension of a clinical trial or infringements</td>
</tr>
<tr>
<td>13</td>
<td>§ 4</td>
<td></td>
<td>Manufacture and import of IMPs</td>
</tr>
<tr>
<td>14</td>
<td>§ 5</td>
<td></td>
<td>Labelling</td>
</tr>
<tr>
<td>15</td>
<td>§ 14</td>
<td></td>
<td>Verification of compliance of IMPs GCP + GMP</td>
</tr>
<tr>
<td>16, 17, 18</td>
<td>§12, 13</td>
<td></td>
<td>Notification of adverse events + serious adverse reactions</td>
</tr>
</tbody>
</table>
Sixth chapter

Protection of human beings during clinical trials

§ 40 General preconditions

(1) Conditions to be fulfilled to perform clinical trial
(2) Informed consent of trial subject
(3) Insurance and indemnity in clinical trials
(4) Clinical trials in minors
(5) Availability of a contact point for trial subjects
§ 40 (1) General preconditions

Sponsor, investigators and all staff involved shall perform clinical trials in accordance to the principles of GCP according to Art. 1 (3) der 2001/20/EG.

The clinical trial shall be commenced by the sponsor

- if the competent ethics committee has given a favourable opinion according to § 42 (1)
- and the competent higher authority has granted an authorisation according to § 42 (2).
§ 40 (1) General preconditions
Clinical trials shall only be performed, if and as long as

1. the sponsor is located in EU or in a member state of the EC
2. the risks, which are involved for the person on whom the clinical trial is to be carried out, are medically justifiable when compared with the anticipated relevance of the medicinal product for medical science,
3. the person, on whom the clinical trial is to be carried out, shall
   a) have legal capacity and is in a position to comprehend the nature, significance and scope of the clinical trial and to form a rational intention in the light of these facts
   b) has been informed acc. to subpara 2 sentence 1 and has given written consent, if not specified differently in subpara 4 or § 41
§ 40 (1) General preconditions
Clinical trials shall only be performed, if and as long as

4. The person, on whom the clinical trial is to be carried out, has not been committed to an institution by virtue of an order issued either by juridical or administrative authorities,

5. *It will be performed in a qualified facility by an investigator in charge, who can prove an adequate qualification; an investigator, a principle investigator* or coordinating investigator should prove at least *two years experience* in the field of clinical trials

6. an *appropriate pharmacological-toxicological investigation* has been carried out which is in compliance with the prevailing standard of scientific knowledge,
Implementation in Germany

12. Revision German AMG (Draft)

§ 40 (1) General preconditions
Clinical trials shall only be performed, if and as long as

7. the investigator and if existing the principle investigator and if existing the coordinating investigator have been informed by a scientist which is responsible for the pharmacological-toxicological test about the findings of said test and the risks to be anticipated with the clinical trial,

8. in the event that a person is killed or a person´s body or health is injured or impaired in the course of the clinical trial, an insurance policy which also provides benefits when no one else accepts liability for the damage, exists in accordance with the provisions contained in subsection 3.

9. for the medical care given to, and medical decisions made on behalf of subjects shall be the responsibility of an appropriately qualified doctor or, where appropriate, of a dentist.
§ 41 Special preconditions

(1) Conditions to be fulfilled for clinical trials with adult subjects be able to give informed consent and suffering from a disease

(2) Conditions to be fulfilled for clinical trials with minors suffering from a disease (Dir.2001/20/EC Art. 4)

(3) Conditions to be fulfilled for clinical trials with adult subjects be incapable to give consent and are suffering from a disease (Dir.2001/20/EC Art. 5)
Implementation in Germany

12. Revision German AMG (Draft)

§ 42 Procedure of the Ethics committee, authorisation at the competent Higher Federal Authority (BfArM, Bonn or Paul-Ehrlich-Institute, Langen)

(1) Application to EC:
Conditions and reasons for non acceptance

(2) Request for an authorisation to the competent Higher Federal Authority:
Conditions and reasons for non acceptance

(3) Federal Ministry of Health and Social Security takes provisions by an ordinance to ensure the proper conduct of clinical trials
§ 42 (1) Procedure of the Ethics committee

- The Sponsor shall submit a valid request for an opinion to the competent EC.

- Only this EC is competent,
  - which is formed according to the law of the ´Bundesland´ (federal states)
  - in which the ´Leiter der klinischen Prüfung´ in Germany is a member of the ´Ärztekammer´ (Chamber of Physicians).

- If there is no ´Leiter der klinischen Prüfung´ in Germany the competent EC will be determined by the site
  - of the principal investigator
  - or there is no principal investigator by the site of the investigator.

- List of German ECs: http://www.bfarm.de
Procedure of the Ethics Committee
Situation according to the current legislation

56 Ethics committees formed according to ´Länder-Law`: 
• 20 ECs of the Medical Practitioner Association in the ´Bundesländer´
• 36 ECs of the Medical Faculties of Universities and Medical High Schools

Requirements according to GDL
Favourable opinion of the EC which is competent for the coordinating investigator in Germany

Requirements according to professional law for MDs:
Each investigator should to be consulted by the concerned EC.

Note
• no time limits for application and review procedure of EC
• risk of several discordant opinions in multi-centre trials
Procedure for a single EC-opinion in a multi-centre trial
§ 41 (1) 12. Revision German AMG (Draft) § 8 Ordinance on GCP (Draft)

Sponsor provides a valid application to all concerned Ethics Committees

EC1, EC2, ECi, EC3, ECxi provide comments within 30 days to EC of coord. invest.

Single opinion provided by EC of coord. invest. within 60 days

Copy to competent authority
Weg zum Votum der Etikkommission

§ 41 (1) 12. Novelle zum AMG und § 8 des GCP Verordnungsentwurf

Der Sponsor sendet je einen kompletten Antrag an alle betroffenen ECs

Die EC1-x senden ihre Kommentare bis Tag 30 zur Leit-EC

Die Leit-EC sendet ihr Votum( single opinion) bis Tag 60 an den Sponsor

Sponsor

Sendet das Votum an die BOB
Procedure for a single EC-opinion
§ 41 (1) 12. Revision German AMG (Draft) § 7 (2) GCP-Ordinance (draft)

Application Receipt

Application not valid

Additional documentation or justification

10 days

14 days

Review on completeness
Weg zum Votum der Etikkommission
§ 41 (1) 12. Novelle zum AMG und § 7(2) des GCP Verordnungsentwurf

Antragseingang

Unvollständig

Zusätzliche Dokumente oder Erklärungen

10 Tage

14 Tage

Vollständigkeitsprüfung
§ 42 (1) Procedure for a single EC-opinion

Conditions and grounds for non acceptance

§ 41 (1) 12. Revision German AMG (Draft) § 7 (2) GCP-Ordinance (draft)

Demands on a valid request:

• ENTR/F2/BL D(2003) *Detailed guidance to be submitted in an application for an EC opinion on the clinical trial on medicinal products for human use:*
  - form which is proposed in this guideline,
  - complete documentation which receive the competent authority, *but without* the detailed documentation about GMP-compliance, pharmaceutical quality and manufacture of the IMP

• Details will be regulated by the `Ordinance´ accord. to § 42 and by the *Announcement* of the BfArM / PEI and the ECs.
**Procedure for a single ethics committee opinion**

§ 42 (1) 12. Revision German AMG (Draft) § 8 Ordinance on GCP (draft)

**Review:**
According to the prevailing standard of scientific knowledge:
- completeness of the preclinical documents
- protocol, investigators brochure, modalities on the recruitment of trial subjects
- informed consent

**Note:**
- Time limit 90 days in clinical trials investigating Gentransfer, somatic cell therapy, genetically modified organisms
- Extended to 180 days if external experts are consulted

<table>
<thead>
<tr>
<th>Multi-centre trials:</th>
<th>60 days</th>
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</thead>
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<tr>
<td>Single-centre trials (incl. 1. step phase I trials):</td>
<td>30 days</td>
</tr>
<tr>
<td>Phase I trials (second + further trials):</td>
<td>14 days</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Receipt of Application (valid)</th>
<th>reasons for non-acceptance</th>
<th>Receipt of additional documents</th>
<th>Acceptance or reasons for non-acceptance (final)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clock stop</td>
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</tbody>
</table>

Note:
- Time limit 90 days in clinical trials investigating Gentransfer, somatic cell therapy, genetically modified organisms
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Review:
According to the prevailing standard of scientific knowledge:
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• protocol, investigators brochure, modalities on the recruitment of trial subjects
• informed consent

Note:
• Time limit 90 days in clinical trials investigating Gentransfer, somatic cell therapy, genetically modified organisms
• Extended to 180 days if external experts are consulted
Conditions and grounds for non acceptance:

- The favourable opinion of the EC can only be refused, if
  - the documentation is incomplete,
  - the documentation, inclusively the trial protocol, the investigator’s brochure and the modalities of the inclusion of the participants are out of the state of scientific knowledge,
  - or do not fulfill the general preconditions for clinical trials according to § 40 (1).
Application to the Ethics Committee

§ 6 (2) Ordinance on GCP (draft)

1. Covering letter by sponsor
2. Form according to the ´Guidance … for an EC opinion´ No. 7.3
3. Explanation concerning the relevance of the clinical trial
4. Evaluation on the anticipated risks and disadvantages versus the expected benefit for the trial subjects and future patients
5. Protocol
6. Explanation on the recruitment of trial subjects especially taking into consideration age and gender adequate for the trial
7. Investigators Brochure
8. Justification for the inclusion of incapacitated subjects, if applicable
9. Name and address of the investigators
10. Information on the qualification of the investigators and their staff
11. Information on other personnel involved in the clinical trial
12. Information on the quality of the trial site
13. Complete overview of the information to be given to the trial subjects and the procedure to be followed for the purpose of obtaining informed consent
Application to the Ethics Committee

§ 6 (2) Ordinance on GCP (draft) (Continued)

13. Provisions for indemnity or compensation in the event of injury or death attributable to a clinical trial

14. Provisions for insurance or indemnity to cover the liability of the investigator and sponsor

15. Arrangements concerning the rewarding of the investigator and compensation of the trial subjects

16. All relevant points concerning the designated contract between sponsor and trial site

17. Statement that the relevant Note for guidances of the EMEA for the evaluation of medicinal products will be followed

18. Copy of the agreements between Sponsor and trial site

19. In multi-center trials list of names and addresses of ethic committees which received an application

20. Further documentation according to ‘Detailed guidance for the application of a clinical trial on a medicinal product for human use to ethics committee, if applicable’
Request for Authorisation to the Competent Authority
Situation according to the current legislation

2 Competent Federal Higher Authorities accord. § 77 AMG
• Federal Institute for Medicines and Medical devices (BfArM in Bonn)
• Paul-Ehrlich Institute, in Langen (PEI in Langen)

Submission procedure for each clinical trial with investigational medicinal products which is not approved in Germany (§ 40 (1) no. 6)
• Documentation on the pharmacological-toxicological studies
• Trial protocol
• Names of the investigators and sites where the trial will be carried out
• Opinion of EC competent for the coordinating investigator

Responsibilities of the BfArM/PEI:
• Control on completeness and archive submitted documentation
• Act as second instance in case of a non favourable opinion
• Collection of all notifications on suspected serious drug reactions
§ 42 (2)
The required authorisation according to § 40 (1) sentence 2 has to be applied for by the sponsor at the competent higher authority.

The sponsor has to submit all information and documentation needed by the competent higher authority for the evaluation (Results

Authorisation shall be denied only, if

1. the submitted documents are incomplete

2. the submitted documents, especially concerning the information on the IMP and the protocol including the investigators brochure are not at the prevailing standard of knowledge

3. the requirements according to § 40 (1) sentence 3 No. 1, 2 and 6, in case of xenogenic cell therapy also requirement No. 8 are not fulfilled

Authorisation can be considered as granted if BfArM / PEI has not provided grounds for non-acceptance within at least 30 days.
Request for Authorisation to the Competent Authority
Explicit authorisation` § 40 (2) 12. Revision German AMG (Draft)

Different from sentence 1 a clinical trial with medicinal products which
- refer to Part A of the Annex of 2309/93/EEC
- are somatic cell therapy, xenogenic cell therapy, medicinal products for
gene therapy
- medicinal products containing genetically modified organisms
- active substance is a biological product of human or animal origen or
contains biological components of human or animal origin, or the
manufacturing of which requires such components

shall only be commenced, if the competent Federal Higher Authority
has granted a written authorisation to the sponsor.

The competent higher authority has take a decision within 60 days,
which can be extended in ordinance acc. to § 42 (3).

No time limit to authorisation period is given for clinical trials with
xenogenic cell therapy.
Request for Authorisation to the Competent Authority

§ 6 (3) Ordinance on GCP (draft)

1. Covering letter by sponsor
2. Application format, Annex 1 `Guidance for request … to the CA …`
3. Protocol
4. Investigators Brochure
5. For multicenter trials name and address of the ethics committee in charge and name and address of the competent authorities in other Member States, if applicable
6. Further documentation according to the `Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to competent authorities`
7. Data on the Investigational Medicinal Product
   a) Manufacturing authorisation
   b) Import license
   c) Documentation on quality and manufacturing according to GMP
   d) Documentation on toxicological and pharmacological studies
   e) Clinical information
   f) Sample of the labelling
   g) Results on contemporary and previously performed clinical trials
Request for Authorisation to the Competent Authority
Announcement BfArM, PEI (publication 2004)

Providing guidance concerning content and format of the request of an authorisation to the competent Federal Higher Authority.

a) Application format (Detailed guidance acc. to Art. 9 (8), 2001/20/EC)

b) Data on the IMPD: (investigational medicinal product dossier)
   • documentation on quality and manufacturing
   • documentation on pharmacological and toxicological studies (ICH M3)
   • documentation on clinical trials or information, if available
   • results on clinical trials

Content of the IMPD depends on the developmental status or on the approval status of the IMP, especially from:
• phase of the clinical trial
• inclusion and exclusion criteria at the trial protocol
• duration of the treatment with the IMP according to the trial protocol
Request for Authorisation to the Competent Authority

§ 41 (2) 12. Revision German AMG (Draft) § 8 GCP-Ordinance (draft)

Request Receipt

Request not valid

Additional documentation or justification

10 days

14 days

Review on completeness
- Covering letter
  (Eudract Nr.)
- Application form
- IMP Dossier
- Investigators brochure
- Protocol
- Certificates
Request for Authorisation to the Competent Authority

(6) § 41 (2) 12. Revision German AMG (Draft) § 8 Ordinance on GCP (draft)

Receipt of Request (complete)

Reasons for non-acceptance (30 days) otherwise accepted

Receipt of additional documents

Acceptance or reasons for non-acceptance (final)

30 days
14 days* 60 days**

90 days

15 days

Review
According to the prevailing standard of scientific knowledge:
• Quality
  - Drug substance
  - Drug product
• pharm-tox. documentation
• clinical documentation

Note
* 15 d 2nd + further trials in phase I
** time limit 60 d in clinical trials investigating medicinal products for gene therapy, somatic cell therapy or medicinal products containing genetically modified organisms
Time period may be extended to max. 180 days if EC has to consult external expert groups
§ 42 (2) Request for an authorisation to the competent higher federal authority: Conditions and reasons for non-acceptance

The authorisation by the ‘BOB*’ can only be refused, if

- the documentation is incomplete, especially the information about the IMP
- the documentation, inclusively the trial protocol, the investigator’s brochure and the modalities of the inclusion of the participants in the trial are out of the state of scientific knowledge
- or do not fulfill the general conditions for clinical trials according to § 40 (1).

* Higher federal authority (e.g. BfArM, PEI)
Demands on a valid request:

- **ENTR/F2/BL D(2003)** *Detailed guidance for the request for authorisation of a clinical trial on a IMP for human use to the competent authorities, notification of substantial amendments and declaration of the end of trial.*
  - form which is proposed in this guideline, Annex 1
  - the complete documentation which receive the 'BOB', but with the detailed documentation about the GMP-compliance, the pharmaceutical quality and the manufacture of the IMP

- **Details** will be regulated by the 'Ordinance' according to §42 and by the 'Announcement of the BfArM / PEI and the ECs'.
Demands on a valid request:
ENTR/F2/BL D(2003) **Detailed guidance for the request for authorisation of a clinical trial on a IMP for human use to the competent authorities, notification of substantial amendments and declaration of the end of trial.**

4.1.5 **Investigators Brochure**

( CPMP/ICH/135/95 *NfG on GCP*)

4.1.6 **Investigational Medicinal Product Dossier (IMPD)***

4.1.6.1 **Full IMPD**
4.6.1.1 Quality data
4.6.1.2 Non-clinical pharmacology and toxicology data
4.6.1.3 Previous clinical trial and human experience data
4.1.6.4 Overall risk and benefit assessment

4.1.6.2 **Simplified IMPD**
<table>
<thead>
<tr>
<th>S: drug subst.data; P: Drug product data</th>
<th>Quality Data</th>
<th>Non Clinical Data</th>
<th>Clinical Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Appendices of the IMPD; SmPC: SPC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The IMP has a <strong>MA</strong> in any EU MS is and used in the trial:</td>
<td>SmPC SmPC S + P + A</td>
<td>SmPC YES if appropriate</td>
<td>SmPC YES if appropriate</td>
</tr>
<tr>
<td>- Within the conditions of the SmPC</td>
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<tr>
<td>- Outside the conditions of the SmPC</td>
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<tr>
<td>- With a change of the drug substance manufacture or manufacturer</td>
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</tr>
<tr>
<td>Another pharmaceutical form or strength of the IMP has a MA in any EU Ms and:</td>
<td>P + A</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>- The IMP is supplied by the MAH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The IMP has a <strong>no MA</strong> in any EU MS but drug substance is authorised in a MS and:</td>
<td>P+A S+P+A</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>- Is supplied from the same manufacturer</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>- Is supplied from another manufacturer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The IMP has a <strong>previous CTA</strong> in the MS(s) concerned:</td>
<td>NO NEW DATA</td>
<td>NO NEW DATA</td>
<td>NO NEW DATA</td>
</tr>
<tr>
<td>- No new data available since CTA</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>- New data available since CTA</td>
<td></td>
<td></td>
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</table>

**Legend:**
- **SmPC:** SPC
- **P + A:** Appendices of the IMPD
- **NO NEW DATA:** NO NEW DATA
Clinical Trials Authorisation Procedure
Task´s of the Competent Authority - BfArM´s View

The minimal tasks´ in this procedure are to check the submitted documents for inacceptable risks which can be caused by

- insufficient analytical or preclinical investigation
- pharmacological-toxicological characteristics of the active substance /-s
- by an insufficient quality of the IMP/-s
- by in insufficient investigation in previous clinical phases.

Possible Risks have to be evaluated always in connection with the trial protocol
(e.g. inclusion-, exclusion criteria, dosage schedule, duration of the treatment, nature and timing of control measures for surveillance of risks, reversibility of risks).

Possible risks should to be sufficiently covered by the trial Protocol and explained in the investigator´s brochure.
Implementation of 2001/20/EG in Germany
Tasks of ethics committee and competent authority

<table>
<thead>
<tr>
<th>Ethics committee</th>
<th>Competent higher authority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review following documentation concerning the prevailing standard of scientific knowledge</td>
<td>Review following documentation concerning the prevailing standard of scientific knowledge</td>
</tr>
<tr>
<td>• Trial protocol, investigators brochure</td>
<td>• Protocol</td>
</tr>
<tr>
<td>• Protection of health and rights of trial subjects:</td>
<td>• Investigators brochure</td>
</tr>
<tr>
<td>• insurance, indemnity</td>
<td>• Documentation on the investigational medicinal product:</td>
</tr>
<tr>
<td>• informed consent</td>
<td>• Manufacturing accord. GMP</td>
</tr>
<tr>
<td>• recruitment</td>
<td>• Quality</td>
</tr>
<tr>
<td>• Qualification of investigators and involved staff</td>
<td>• Pharm. tox. studies</td>
</tr>
<tr>
<td>• Qualification of each trial site</td>
<td>• Clinical information</td>
</tr>
<tr>
<td>• Financial agreements</td>
<td>• Labelling</td>
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### Future Clinical Trials Authorisation Procedure

#### Consequences – time limits

<table>
<thead>
<tr>
<th>Ethics Commission Opinion</th>
<th>Competent Authority Decision</th>
<th>Clinical Trial</th>
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<tbody>
<tr>
<td>favourable</td>
<td>no reasons for no-acceptance</td>
<td>approved</td>
</tr>
<tr>
<td>favourable</td>
<td>reasons for non-acceptance</td>
<td>disapproved</td>
</tr>
<tr>
<td>negative</td>
<td>no reasons for non-acceptance</td>
<td>disapproved</td>
</tr>
<tr>
<td>negative</td>
<td>reasons for non-acceptance</td>
<td>disapproved</td>
</tr>
<tr>
<td>stop clock procedure</td>
<td>no stop clock procedure</td>
<td></td>
</tr>
</tbody>
</table>
Request for Authorisation to the Competent Authority

§ 9 Ordinance on GCP (draft, 02.09.2003)

Notification of substantial amendments to the trial protocol

- `Substantial` where they are likely to have a significant impact on:
  - the safety or physical or mental integrity of subjects
  - the scientific value of the trial
  - the conduct or management of the trial
  - the quality or safety of any IMP used in the trial.

- Notification to the competent EC and the competent Federal Higher Authority
  - Opinion of the EC within 20 (35) days and an implicit or explicit approval by the competent FA within 20 (35) days.

- Investigator or sponsor shall immediately introduce measures in urgent safety circumstances and the sponsor shall immediately notify the changes of the trial protocol to the competent EC and the competent FA.
Request for Authorisation to the Competent Authority

§ 9 Ordinance on GCP (draft, 02.09.2003)

Notification of the end of a clinical trial by the sponsor:

- Regularly end:
  
  within 90 days

- If the trial is to be terminated early:
  
  within 15 days,
  reasons shall be clearly explained
Pharmacovigilance in clinical trials
Notification acc. §§ 12, 13 Ordinance on GCP (draft)

Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use
Pharmacovigilance in clinical trials

Notification scheme acc. §§ 12, 13 Ordinance on GCP (draft)

---

**Investigators**

- **All SAE**
- Critical AE, lab. abnormalities acc. to protocol

---

**Sponsor**

- **All SUSAR**
- Information on death of a subject

---

**Ethics Committee**

- **All SUSAR**
- Annual report

---

**Competent Authority**

- **All SUSAR**
- All SAE (on request)
- Annual report

---
### Summary Pharmacovigilance in clinical trials

<table>
<thead>
<tr>
<th>Current situation</th>
</tr>
</thead>
<tbody>
<tr>
<td>§ 29 subpara 1 sentence 2-6 i.c.w. 8 GML</td>
</tr>
<tr>
<td>§ 40 subpara 1 sentence 4 GML</td>
</tr>
<tr>
<td>3. Announcement BfArM, PEI (15.05.1996)</td>
</tr>
<tr>
<td>Responsibilities and notifying person not clearly defined</td>
</tr>
<tr>
<td>Notification to competent authority:</td>
</tr>
<tr>
<td>• all SAR</td>
</tr>
<tr>
<td>Time limit for SAR: 14 days</td>
</tr>
<tr>
<td>Notification to EC: AE (serious or unexpected with a possible impact on the risk of probands/patients or the further performance of the clinical trial)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Future situation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ordinance §§ 12, 42 acc. to 12. Revision GML</td>
</tr>
<tr>
<td>Guidances according to Art. 18 of 2001/20EC</td>
</tr>
<tr>
<td>Responsibilities and notifying person clearly defined</td>
</tr>
<tr>
<td>Notification to competent authority:</td>
</tr>
<tr>
<td>• all SUSARs</td>
</tr>
<tr>
<td>• other safety issues</td>
</tr>
<tr>
<td>• Annual Safety Report</td>
</tr>
<tr>
<td>Time limit for SUSAR: 7 or 14 days</td>
</tr>
<tr>
<td>Notification EC: SUSUR in MS</td>
</tr>
<tr>
<td>Annual safety report</td>
</tr>
<tr>
<td>Sponsor informs investigators</td>
</tr>
</tbody>
</table>
§ 42a Withdrawal, revocation and suspension of the authorisation (Dir. 2001/20/EC Art. 12)

(1) Defines reasons under which the competent higher authority has to revoke or withdraw the authorisation

(2) Defines grounds under which the competent higher authority has to withdraw or suspend the authorisation

(3) Need for a hearing of the sponsor before taking a decision acc. (1) and (2)

(4) If authorisation of a clinical trial has been withdrawn, revoked or suspended, the clinical should not be continued.

(5) If the competent higher authority assumes that the sponsor, investigator or other staff involved do not fulfil the requirements concerning the proper conduct of the clinical trial, the competent higher authority shall immediately inform the concerned person and arrange the measures to be taken by the concerned person
Consequences of the Implementation of the Directive 2001/20/E in Germany

1. A complete reorganisation of the procedures of ECs

2. Implementation and organisation of the approval procedure by both ´BOBs´:
   - approval procedure for each clinical trial, including substantial amendments
     (algorithms for minimal requirements for documentation which is necessary in dependence of the Phase of development or the marketing status of an IMP)
   - procedures for a systematic surveillance of clinical trials and introduction of measures according to Article 12 of the Dir. 2001/20/EC
   - recruiting and training of the new personal

3. Reorganisation of the competence and procedures for GCP-Inspections in Germany.
but in reality the piggies never would hurt their sweetheart „sai mai“. The tiger was breast-fed by a hog when she was a baby.

This is the Win-Win-Situation

had this pitifully bengal tiger having been attacked by these „bloodthirsty piglets“

Thank you for your kind attention
• For information/discussion only
<table>
<thead>
<tr>
<th>S: drug subst.data; P: Drug product data</th>
<th>A: Appendices of the IMPD; SmPC: SPC</th>
<th>Quality Data</th>
<th>Non Clinical Data</th>
<th>Clinical Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>The IMP has a MA in any EU MS is and used in the trial:</td>
<td></td>
<td>SmPC SmPC S + P + A</td>
<td>SmPC YES if appropriate</td>
<td>SmPC YES if appropriate</td>
</tr>
<tr>
<td>- Within the conditions of the SmPC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Outside the conditions of the SmPC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- With a change of the drug substance manufacture or manufacturer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Another pharmaceutical form or strength of the IMP has a MA in any EU Ms and:</td>
<td></td>
<td>P + A</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>- The IMP is supplied by the MAH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The IMP has a no MA in any EU MS but drug substance is authorised in a MS and:</td>
<td></td>
<td>P+ A S + P + A</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>- Is supplied from the same manufacturer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Is supplied from another manufacturer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The IMP has a previous CTA in the MS(s) concerned:</td>
<td></td>
<td>NO NEW DATA</td>
<td>NO NEW DATA</td>
<td>NO NEW DATA</td>
</tr>
<tr>
<td>- No new data available since CTA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- New data available since CTA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### IMPD
Non clinical pharmacology and toxicology data

<table>
<thead>
<tr>
<th>Pharmacology Pharmacodynamics</th>
<th>Phase Ia single dose increasing</th>
<th>Phase Ib multiple d. increasing</th>
<th>Phase IIa multiple d increasing</th>
<th>Phase IIb multiple d increasing</th>
<th>Phase III multiple d increasing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Primary Pharmacodynamics</td>
<td>+</td>
<td>+ (additional Investations)</td>
<td>+ (additional Investations)</td>
<td>+ (additional Investations)</td>
<td>+ (additional Investations)</td>
</tr>
<tr>
<td>2. Sekundary Pharmacodynamics</td>
<td>+</td>
<td>+ (additional Investations)</td>
<td>+ (additional Investations)</td>
<td>+ (additional Investations)</td>
<td>+ (additional Investations)</td>
</tr>
<tr>
<td>3. Safety pharmacology</td>
<td>+</td>
<td>+ (additional Investations)</td>
<td>+ (additional Investations)</td>
<td>+ (additional Investations)</td>
<td>+ (additional Investations)</td>
</tr>
<tr>
<td>4. Pharmacodynamical interactions</td>
<td>(+) (if part of the clinical trial)</td>
<td>(+) (if part of the clinical trial)</td>
<td>+ (if concomittant therapy)</td>
<td>+ (if concomittant therapy)</td>
<td>+ (if concomittant therapy)</td>
</tr>
<tr>
<td>5. Overall risk and benefit assessment</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
Pharmacodynamics

- primary and sekundary pharmakodynamic
- safety pharmacology
  CPMP/ICH/539/95, mod.
  NfG on Safety Pharmacology Studies for Human Pharmaceuticals
  ✔ CNS
  ✔ cardio-vaskulrary system
    CPMP/ICH/423/02
    NfG on Safety Pharmacology Studies for assessing the Potential for Delayed Ventricular Repolarisation (QT Interval Prolongation) by Human Pharmaceuticals
  ✔ respiratory system
  ✔ additional systems, depending from the characteristics of the active substance:
    - renal system
    - autonomic NS
    - gastrointestinal system
    - other functional systems
Pharmacodynamics

Assessment of the results:

- Relevanz of the models, in vitro (subcellular, cellular, isolated organs) and in vivo, effects in dependence from the species
- in vitro - concentration-effect-relations
- in vivo - dose effect- and time-effect-relations
- therapeutic range
- correlation with the pharmacocinetics
- comparision with active substances with well known effects according to affinity and intrinsic activity
<table>
<thead>
<tr>
<th>Toxicology</th>
<th>Phase Ia ED aufsteigend</th>
<th>Phase Ib multiple D aufsteigend</th>
<th>Phase IIa multiple D aufsteigend</th>
<th>Phase IIb multiple D aufsteigend</th>
<th>Phase III multiple D</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Single dose toxicity</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>2. Repeated dose toxicity</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>3. Genotoxicity:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.1 in vitro (men´s)</td>
<td>+ (Männer)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>3.2 in vivo (women)</td>
<td>( + Frauen )</td>
<td>( + Frauen)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Toxizität auf die Reproduktion</td>
<td>/ exclusion of women in generative age</td>
<td>/ exclusion of women in generative age</td>
<td>+ inclusion of women in generative age</td>
<td>+ inclusion of women in generative age</td>
<td>+ inclusion of women in generative age</td>
</tr>
<tr>
<td>6. Karzinogenität</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>7 lokale Toxizität</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>5. Bewertung</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
2 Tierarten, gleiche Anzahl beiderlei Geschlechts:

- 1. Anwendungsart soll der für die klinische Prüfung am Menschen vorgesehenen Anwendung entsprechen,
- 1. Anwendungsart soll iv. bzw. geeignet sein, die Substanz unverändert in den Kreislauf bringen
- Bei Nagetieren sollte die approximative Letalität quantitativ und deren Dosisabhängigkeit
- bestimmt werden.
**Toxizität bei wiederholter Anwendung**

CPMP/ICH/286/95 mod.: *NfG Non-Clinical Safety Studies for Conduct of Human Clin.Trials*

CPMP/ICH/300/95: *NfG on Duration of Chronic Toxicity Testing in Animals (Rodent and Non-Rodent Toxicity Testing)*

CPMP/SWP/1042/99 corr.: *NfG on Repeated Toxicity*

<table>
<thead>
<tr>
<th>Anwendungsdauer am Menschen gemäss Prüfplan</th>
<th>Phase I und II Nichtnager</th>
<th>Phase I und II Nager</th>
<th>Phase III Nager</th>
<th>Phase III Nichtnager</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED</td>
<td>2 Wochen</td>
<td>2 Wochen</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>bis zu 2 Wochen</td>
<td>2 Wochen</td>
<td>2 Wochen</td>
<td>1 Monat</td>
<td>1 Monat</td>
</tr>
<tr>
<td>bis zu 1 Monat</td>
<td>1 Monat</td>
<td>1 Monat</td>
<td>3 Monate</td>
<td>3 Monate</td>
</tr>
<tr>
<td>bis zu 3 Monaten</td>
<td>3 Monate</td>
<td>3 Monate</td>
<td>6 Monate</td>
<td>3 Monate</td>
</tr>
<tr>
<td>über 3 Monate</td>
<td>/</td>
<td>/</td>
<td>6 Monate</td>
<td>chronisch* (9 Monate)</td>
</tr>
<tr>
<td>bis zu 6 Monaten</td>
<td>6 Monate</td>
<td>6 Monate*</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>über 6 Monate</td>
<td>6 Monate</td>
<td>chronisch*</td>
<td>/</td>
<td>/</td>
</tr>
</tbody>
</table>
Genotoxicity

CPMP/ICH/286/95 mod.
NfG Non-Clinical Safety Studies for Conduct of Human Clinical Trials

CPMP/ICH/142/95
NfG on Genotoxicity: Guidance on Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals

CPMP/ICH/174/95
NfG on Genotoxicity: Battery for Genotoxicity Testing of Pharmaceuticals
### Reproduktion

**CPMP/ICH/286/95 mod. NfG on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals**

<table>
<thead>
<tr>
<th>Toxikologie</th>
<th>Phase Ia ED aufsteigend</th>
<th>Phase Ib multiple D aufsteigend</th>
<th>Phase IIa multiple D aufsteigend</th>
<th>Phase IIb multiple D aufsteigend</th>
<th>Phase III multiple D</th>
</tr>
</thead>
<tbody>
<tr>
<td>5. Fertility studies man’s</td>
<td>repeated dose toxicity sufficiently</td>
<td>repeated dose toxicity sufficiently</td>
<td>repeated dose toxicity sufficiently</td>
<td>repeated dose toxicity sufficiently</td>
<td>+ Studie männl. Fertilität</td>
</tr>
<tr>
<td>5.2 women without generative potential (permanently sterilised, postmenopausal)</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>5.3 women with generative potential effektive contraception, failure lesser than ( \leq 1% / J )</td>
<td>? Inclusion + Genotox.</td>
<td>? Inclusion + Genotox.</td>
<td>+ inclusion + Genotox.</td>
<td>+ inclusion + Genotox.</td>
<td>+ inclusion + Genotox.</td>
</tr>
<tr>
<td>5.4 pregnant women</td>
<td>?</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

- **Genotox.**
- **Studie männl. Fertilität**
- **ED**
- **D**
- **Aufsteigend**
- **Multiple**
Reproduktion
CPMP/ICH/286/95 mod. NfG on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals

Women with generative potential:
Phase I:
• Fertility, studies to the embryonal development,
• Toxicity of the reproduktive organ systems (results of the repeated dose toxicity)
• Genotoxicity in vitro und in vivo

Phasen 2 und 3:
• complete reproduction toxicity studies, inclusively peri- und postnatal studies,
• genotoxicity in vitro and in vivo

Women with effektive contraceptive control and careful surveillance:
• possibly inclusion in phase I- and II-studies without complete reproduction studies, if necessary
### Pharmacokinetics

**CPMP/ICH/384/95 NfG on Toxicokinetics: A Guidance for Assessing Systemic Exposure in Toxicological Studies**

<table>
<thead>
<tr>
<th>Single dose, repeated dose</th>
<th>Phase Ia single dose increasing</th>
<th>Phase Ib multiple dose increasing</th>
<th>Phase IIa multiple dose increasing</th>
<th>Phase IIb multiple dose increasing</th>
<th>Phase III multiple dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absorption</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Metabolisation</strong></td>
<td>+ orientierend</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Organs, Tissues, body fluids</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Plasma-protein-binding</strong></td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Toxicokinetiks</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>5. Evaluation</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>