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

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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 importisation 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

Phasen der klinischen Prüfung	Prüfpräparate, die Wirkstoffe enthalten, zu denen es in D bereits zugelassene AM gibt	Prüfpräparate, die Wirkstoffe enthalten, zu denen es in D keine zugelassenen AM gibt	Summen
in Phase I	222	222 / 14%	444 / 28 %
in Phase II	176	159 / 10%	335 / 21 %
in Phase III	297	123 / 8%	420 / 26 %
Zwischensumme Anzahl Prüfpläne	695	504	1199 / 75 %
in Phase IV Schätzung	*401*	/	*401* / 25 %
Summen / %	***1096*** / 68 %	504 / 32 %	***1600*** / 100%

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Implementation in Germany

➢ 12th Revision of the German Drug Law (AMG)

- first draft, dated 25th April 2003, actual governmental draft published 15.10.2003 **(http:// www.bmgs.de)**
- (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)**

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Legal Levels

European Level

Directive 2001/20/EC

´… conduct of Clinical Trials´

Commission Directive

´Principles and Guidelines for GCP´

1

German Level

12. Revision AMG

Ordinance acc. to § 42 AMG

2

Detailed Guidances

1a

Announcement BfArM/PEI/ECs

Detailed Guidances

2a

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Implemtention of 2001/20/EG in the German AMG, (Draft) *Overview*

2001/20/EC	*12. Rev. AMG*	*Ordinance on GCP*	Topics of the Directive 2001/20/EG
1	§ 40	§§ 1, 2	Scope
2	§ 4	§ 3	Definitions
3	§ 41		Protection of clinical trial subjects
4	§41, 2		Clinical trials on minors
5	§41, 3		Clinical trials on incapacitated adults
6, 7, 8	§ 42,1	§§ 6, 7	*Ethics-Committee + single opinion*
9	§ 42,2	§ 8	*Commencement of a clinical trial*
10		§ 9, 11	*Conduct of a clinical trial (including end of trial)*
11		§ 15, 16	*Exchange of information*
12	§42a	§ 10	*Suspension of a clinical trial or infringements*
13		§ 4	*Manufacture and import of IMPs*
14		§ 5	Labelling
15		§ 14	*Verification of compliance of IMPs GCP + GMP*
16, 17, 18		§12, 13	*Notification of adverse events + serious adverse reactions*

12. Revision German AMG (Draft)

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

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Implementation in Germany

12. Revision AMG (Draft)

§ 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).***

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Implementation in Germany

12. Revision German AMG (Draft)

§ 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

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Implementation in Germany

12. Revision German AMG (Draft)

§ 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,

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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.***

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Implementation in Germany

12. Revision German AMG (Draft)

§ 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)*

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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-Insitute, 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

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Implementation in Germany

12. Revision German AMG (Draft)

§ 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 Phsicians).
- 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

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Procedure of the Ethics Committee

Situation according to the current legislation

56 Ethics committees formed according to ´Länder-Law`:

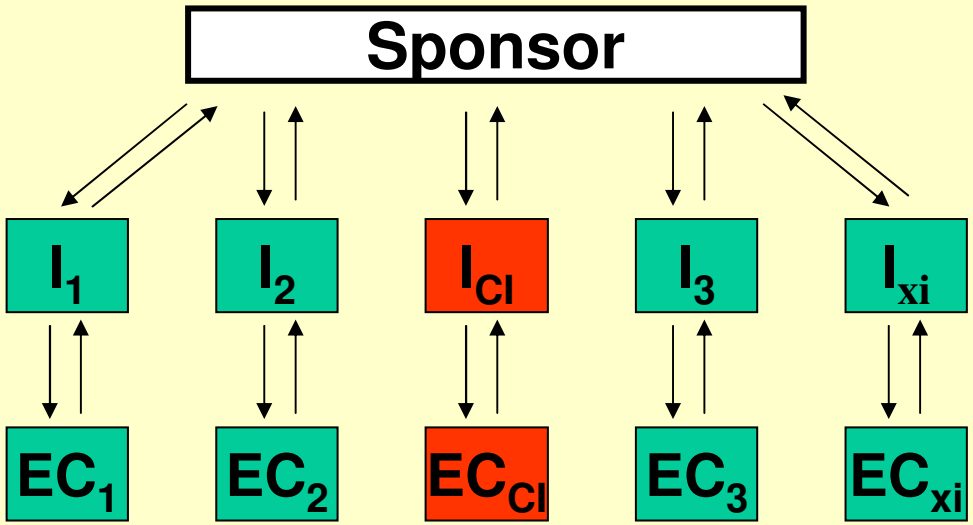
- 20 ECs of the Medical Practioner Association in the ´Bundesländer´
- 36 ECs of the Medical Faculties of Universities and Medical High Schools

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

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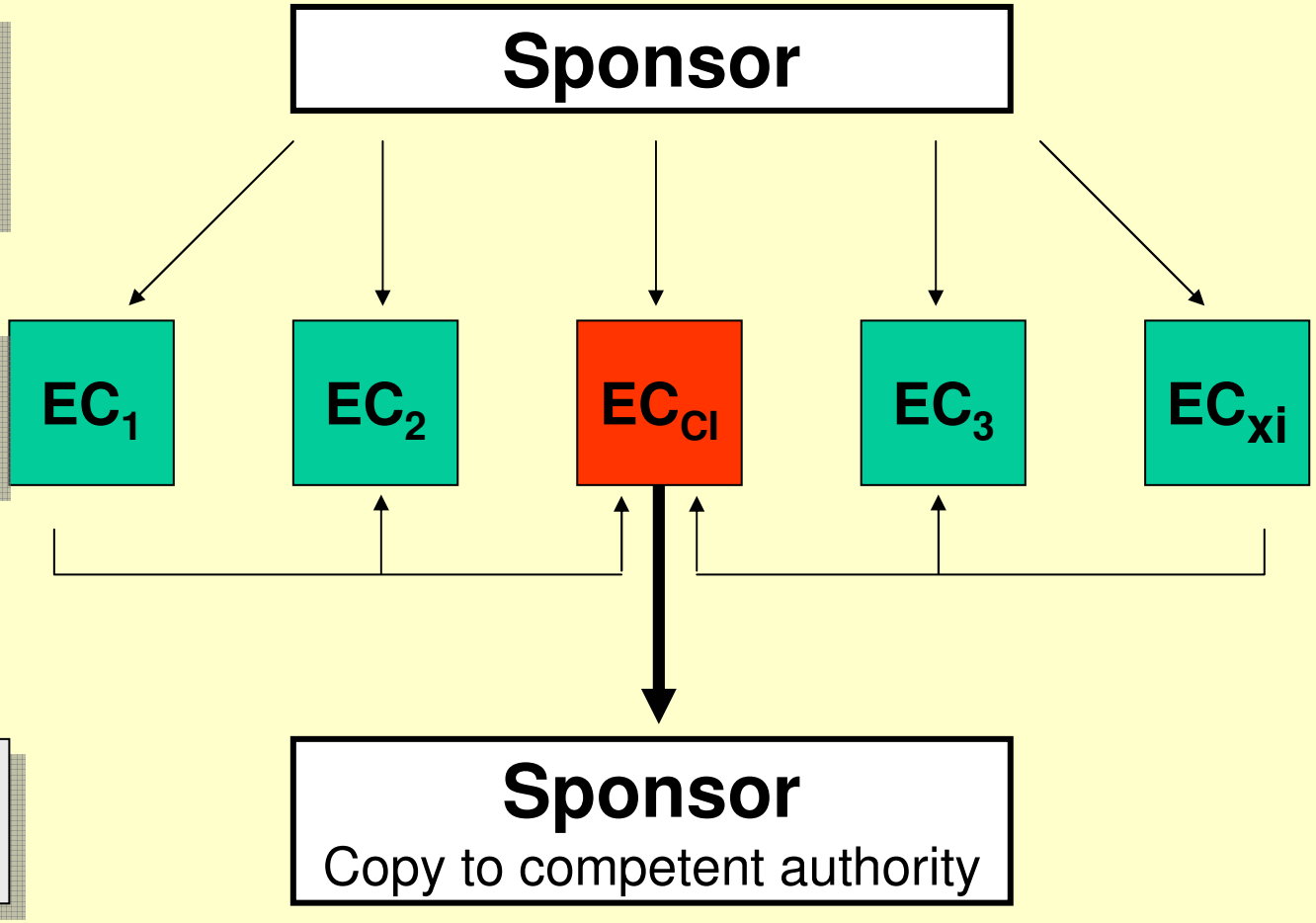
Procedure for a single EC-opinion in a multi-centre trial

§ 41 (1) 12. Revision German AMG (Draft) § 8 Ordinance on GCP (Draft)

Sponsor provides a valid application to all concerned Ethics Committees

EC1-x_i provide comments within 30 days to EC of coord. invest.



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

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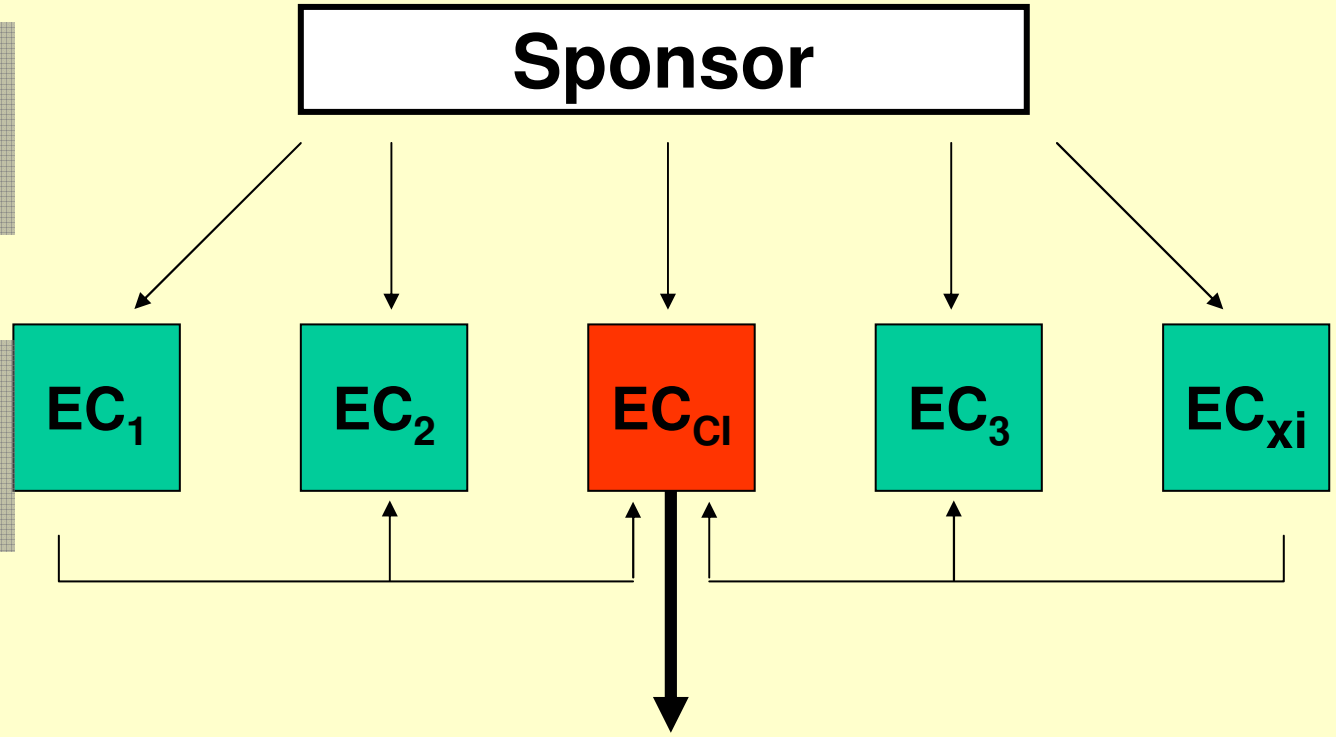
Weg zum Votum der Etikkommission

§ 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_i 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

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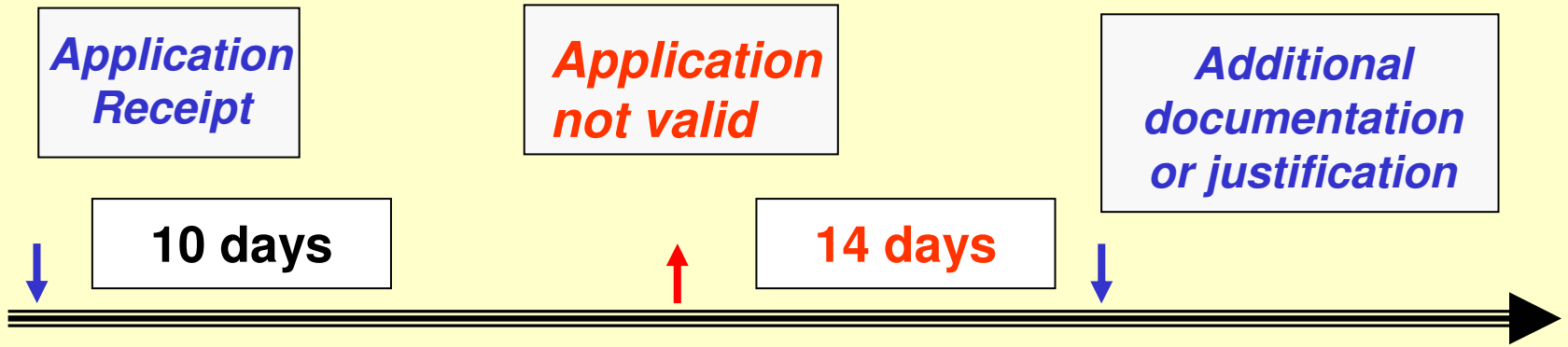
Procedure for a single EC-opinion

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



Review on completeness

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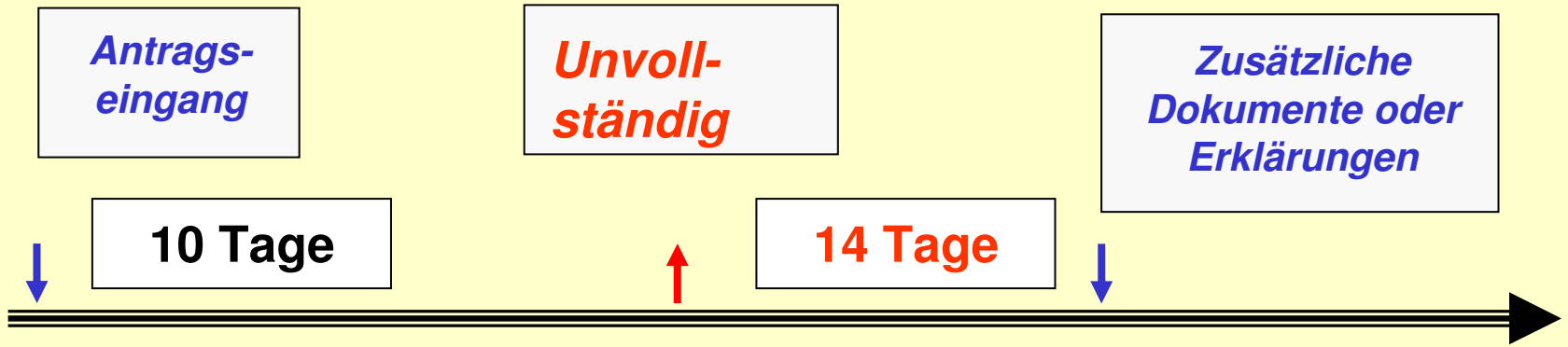
Weg zum Votum der Etikkommission

§ 41 (1) 12. Novelle zum AMG und § 7(2) des GCP Verordnungsentwurf



Vollständigkeitsprüfung

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§ 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.

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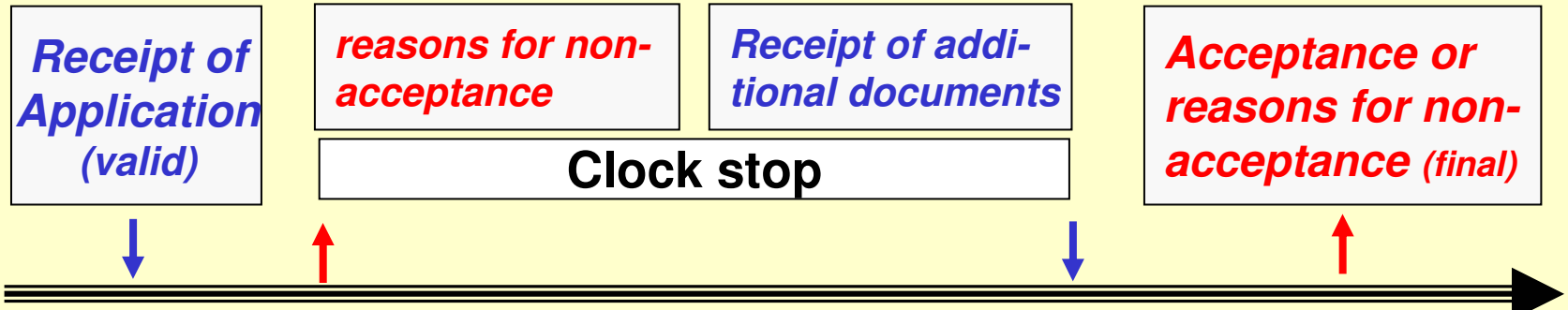
Procedure for a single ethics committee opinion

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



Multi-centre trials:	**60 days**
Single-centre trials (incl. 1. step phase I trials) :	**30 days**
Phase I trials (second + further trials):	**14 days**

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

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Weg zum Votum der Etikkommission

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

Multi-centre trials:	**60 days**
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§ 42 (1) Procedure for a single EC-opinion

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

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).

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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 personel 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

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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 adresses 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´

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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

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Request for Authorisation to the Competent Authority

´Implicit authorisation` 12. Revision German AMG (Draft)

§ 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.

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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.*

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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 adress of the ethics committee in charge and name and adress 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 medi-cinal 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

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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 *(Detailled 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 af the trial protocol*
- *duration of the treatment with the IMP according to the trial protocol*

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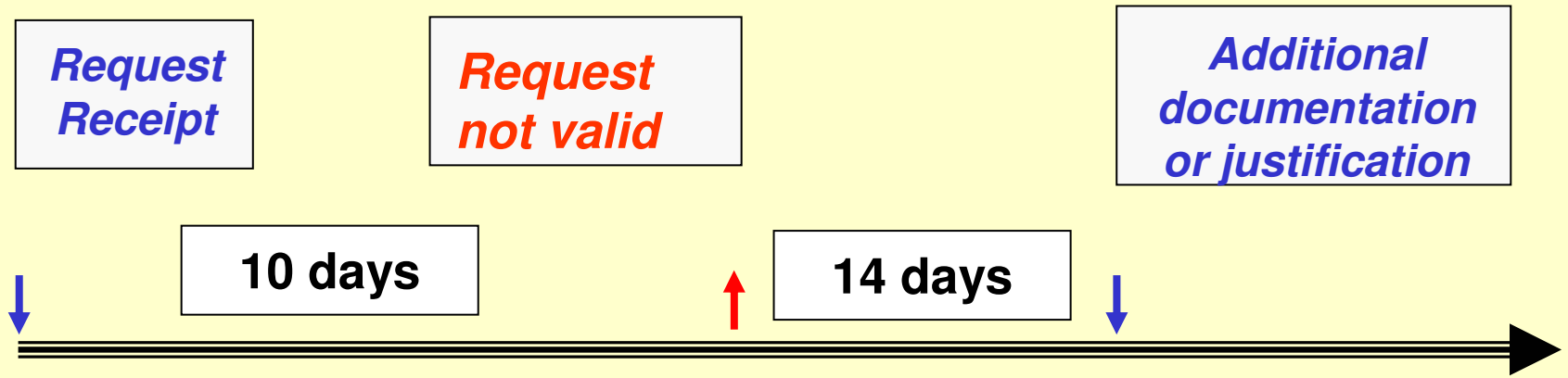
Request for Authorisation to the Competent Authority

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



Review on completeness

- Covering letter
  (Eudract Nr.)
- Application form
- IMP Dossier
- Investigators brochure
- Protocol
- Certificates

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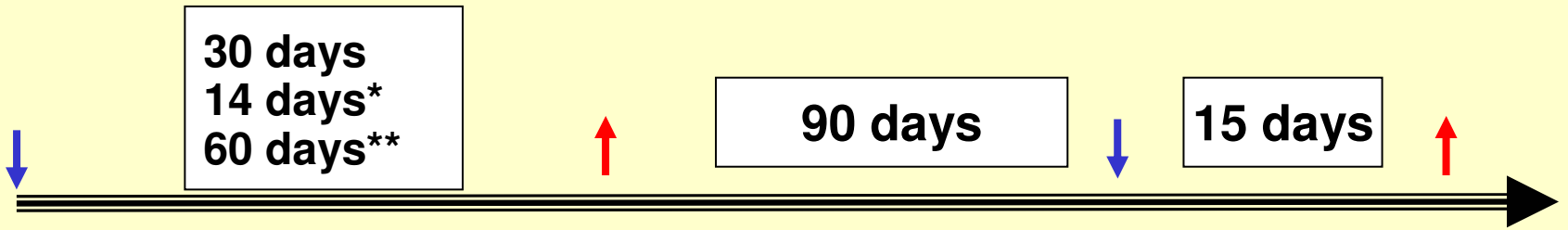
Request for Authorisation to the Competent Authority

(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)*



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

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Implementation in Germany

12. Revision German AMG (Draft) 12. LA GDL, (Draft 25.08.2003)

§ 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)***

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12. Revision German AMG (Draft)

§ 42 GMA – Procedures of the Ethics Committee, Authorisation by the BfArM or PEI

(2) (continue)

➢ **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´.*

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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

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

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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.

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Implementation of 2001/20/EG in Germany

Tasks of ethics committee and competent authority

Ethics committee

Review following documentation concerning the prevailing standard of scientific knowledge

- **Trial protocol, investigators brochure**
- **Protection of health and rights of trial subjects:**
  - **insurance, indemnity**
  - **informed consent**
  - **recruitment**
- **Qualification of investigators and involved staff**
- **Qualification of each trial site**
- **Financial agreements**

Competent higher authority

Review following documentation concerning the prevailing standard of scientific knowledge

- Protocol
- Investigators brochure
- Documentation on the investigational medicinal product:
  - **Manufacturing accord. GMP**
  - **Quality**
  - **Pharm. tox. studies**
  - **Clinical information**
  - **Labelling**

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Article 6, 9, 10

Future Clinical Trials Authorisation Procedure

Consequences – time limits

Ethics Commission Opinion	Competent Authority Decision	Clinical Trial
favourable	no reasons for no-acceptance	approved
favourable	reasons for non-acceptance	disapproved
negative	no reasons for non-acceptance	disapproved
negative	reasons for non-acceptance	disapproved
stop clock procedure	no stop clock procedure	

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Request for Authorisation to the Competent Authority

§ 9 Ordinance on GCP *(draft, 02.09.2003)*

Notification of substantial amendments to the trial protcol

- **`*Substantial*` where they are likely to have a significant impact on:**
  - the safety or phsical 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 implict 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 .**

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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

- ***I the trial ist has to be terminated early:***

  within 15 days,
  reasons shall be clearly explained

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Pharmacovigilance in clinical trials

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

ENTR/F2/BL D(2003) Oct. 2003

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

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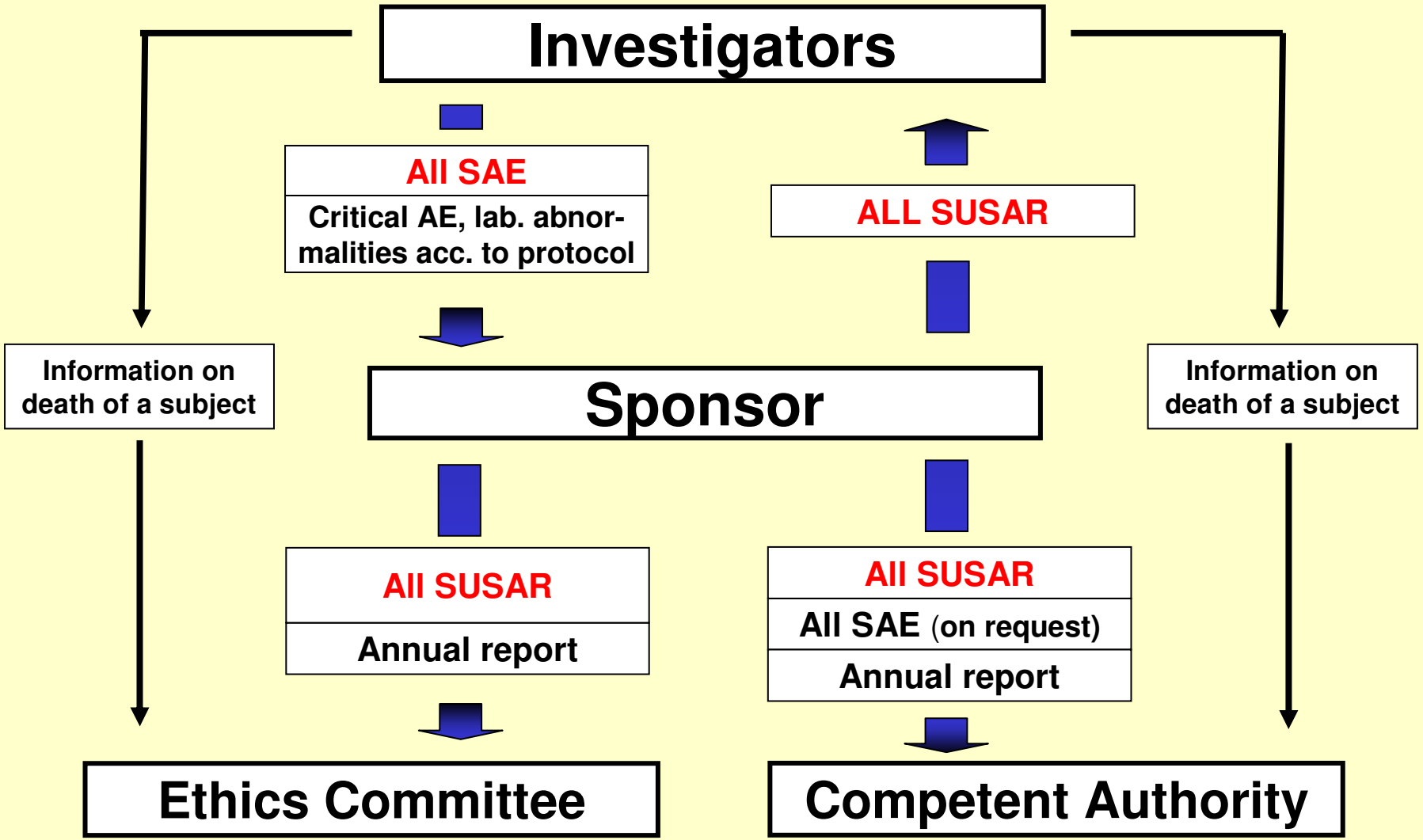
Pharmacovigilance in clinical trials

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



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Summary *Pharmacovigilance in clinical trials*

Current situation	Future situation
§ 29 subpara 1 sentence 2- 6 i.c.w. 8 GML § 40 subpara 1 sentence 4 GML 3. Announcement BfArM, PEI (15.05.1996)	Ordinance §§ 12, 42 acc. to 12. Revision GML Guidances according to Art. 18 of 2001/20EC
Responsibilities and notifying person not clearly defined n	Responsibilities and notifying person clearly defined
Notification to competent authority: • *all SAR*	Notification to competent authority : • *all SUSARs* • *other safety issues* • *Annual Safety Report*
Time limit for SAR: 14 days	Time limit for SUSAR: 7 or 14 d
Notification to EC: AE *(serious or unexpected with a possible impact on the risk of probands/patiens or the further performance of the clinical trial)*	Notification EC: SUSUR in MS *Annual safety report*
	Sponsor informs investigators

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Implementation in Germany

12. Revision German AMG (Draft)

§ 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**

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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.**

Frankfurter Rundschau of 8 May 2003

Agency

Industry

Thank you for your kind attention

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.

had this pitiably bengal tiger having been attact by these „bloodthirsty piglets“

This is the Win-Win-Situation

- **For information/discussion only**

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

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IMPD
Non clinical pharmacology and toxicology data

Pharmacology Pharmacodyna - mics	Phase Ia single dose increasing	Phase Ib multiple d. increasing	Phase IIa multiple d increasing	Phase IIb multiple d increasing	Phase III multiple d
1. Primary Pharmacodynamics	+	+ (additional Investations)	+ (additional Investations)	+ (additional Investations)	+ (additional Investations)
2. sekundary Pharmacodynamics	+	+ (additional Investations)	+ (additional Investations)	+ (additional Investations)	+ (additional Investations)
3. Safety pharmacology	+	+ (additional Investations)	+ (additional Investations)	+ (additional Investations)	+ (additional Investations)
4. pharmakodyna- mical interactions	(+) (if part of the clinical trial)	(+) (if part of the clinical trial)	+ (if conco- mittant therapy)	+ (if conco- mittant therapy)	+ (if conco- mittant therapy)
5. Overall risk and benefit assessment	+	+	+	+	+

Pharmacodynamics

- **primary and sekundary pharmakodynamic**
- **safety pharmacology**

  CPMP/ICH/539/95, mod.
  NfG on Safety Pharmacology Studies for Human Pharmaceuticals

  - ✓ **CNS**
  - ✓ **cardio-vaskulary 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 (subcellurar, cellular, isolated organs) and in vivo,
  effects in dependence from the species
- **in vitro - conzentration- 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**

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Toxicology	Phase Ia ED aufsteigend	Phase Ib multiple D aufsteigend	Phase IIa multiple D aufsteigend	Phase IIb multiple D aufsteigend	Phase III multiple D
1. Single dose toxicity	+	+	+	+	+
2. Repeated dose toxicity	+	+	+	+	+
3. Genotoxicity:					
3.1 in vitro (men´s) 3.2 in vivo (women)	+ (Männer) (+ Frauen)	+ (+ Frauen)	+ +	+ +	+ +
5. Toxizität auf die Reproduktion	/ exclusion of women in generative age	/ exclusion of women in generative age	+ inclusion of women in generative age	+ inclusion of women in generative age	+ inclusion of women in generative age
6. Karzinogenität	/	/	/	/	/
7 lokale Toxizität	+	+	+	+	+
5. Bewertung	+	+	+	+	+

Akute Toxizität - ´single dose toxicity`

Eudralex Vol 2 B

2 Tierarten, gleiche Anzahl beiderlei Geschlechts:

- 1 Anwendungsart soll der für die klinische Prüfung am Menschen vorgesehnen 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.

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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*

Anwendungsdauer am Menschen gemäss Prüfplan	**Phase I und II Nager**	**Phase I und II Nichtnager**	**Phase III Nager**	**Phase III Nichtnager**
ED	**2 Wochen**	**2 Wochen**	/	/
bis zu 2 Wochen	**2 Wochen**	**2 Wochen**	**1 Monat**	**1 Monat**
bis zu 1 Monat	**1 Monat**	**1 Monat**	**3 Monate**	**3 Monate**
bis zu 3 Monaten	**3 Monate**	**3 Monate**	**6 Monate**	**3 Monate**
über 3 Monate	/	/	**6 Monate**	**chronisch*** (9 Monate)
bis zu 6 Monaten	**6 Monate**	**6 Monate***	/	
über 6 Monate	**6 Monate**	**chronisch***	/	/

Genotoxicity

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

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

C**PMP/ICH/174/95**
NfG on Genotoxicity: Battery for Genotoxicity Testing of Pharmaceuticals

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Reproduktion

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

Toxikologie **5. Toxizität auf die Reproduktion**	**Phase Ia** **ED** **aufsteigend**	**Phase Ib** **multiple D** **aufsteigend**	**Phase IIa** **multiple D** **aufsteigend**	**Phase IIb** **multiple D** **aufsteigend**	**Phase III** **multiple D**
5.1 Fertility studies man´s	repeated dose toxicity sufficiently	repeated dose toxicity sufficiently	repeated dose toxicity sufficiently	repeated dose toxicity sufficiently	**+** **Studie männl. Fertilität**
5.2 women without genera-tive potential (permanently steri-lised, postmeno-pausal)	/	/	/	/	/
5.3 women with generative poten-tial effektive contra-ception, failure lesser than ≤ 1%/J)	**?** **Inclusion** **+ Genotox.**	**?** **Inclusion** **+ Genotox.**	**+** **inclusion** **+ Genotox.**	**+** **inclusion** **+ Genotox.**	**+** **inclusion** **+ Genotox.**
5.4 pregnant women	**?** **+ Genotox.**	**?** **+ Genotox.**	**+** **+ Genotox.**	**+** **+ Genotox.**	**+** **+ Genotox.**

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**

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Pharmacokinetics

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

Single dose, repeated dose	Phase Ia single dose increasing	Phase Ib multiple dose increasing	Phase IIa multiple dose increasing	Phase IIb multiple dose increasing	Phase III multiple dose
Absorption	+	+	+	+	+
Distribution	+	+	+	+	+
Metabolisation	+ orientierend	+	+	+	+
Elimination	+	+	+	+	+
Distribution Organs, Tissues, body fluids	+	+	+	+	+
Plasma-protein-binding	+	+	+	+	+
Toxicokinetiks	+	+	+	+	+
5. Evaluation	+	+	+	+	+