# Workshop on drug policy, new pharmaceutical procedures in EC

## Sofia
## 18 – 19 April 2007

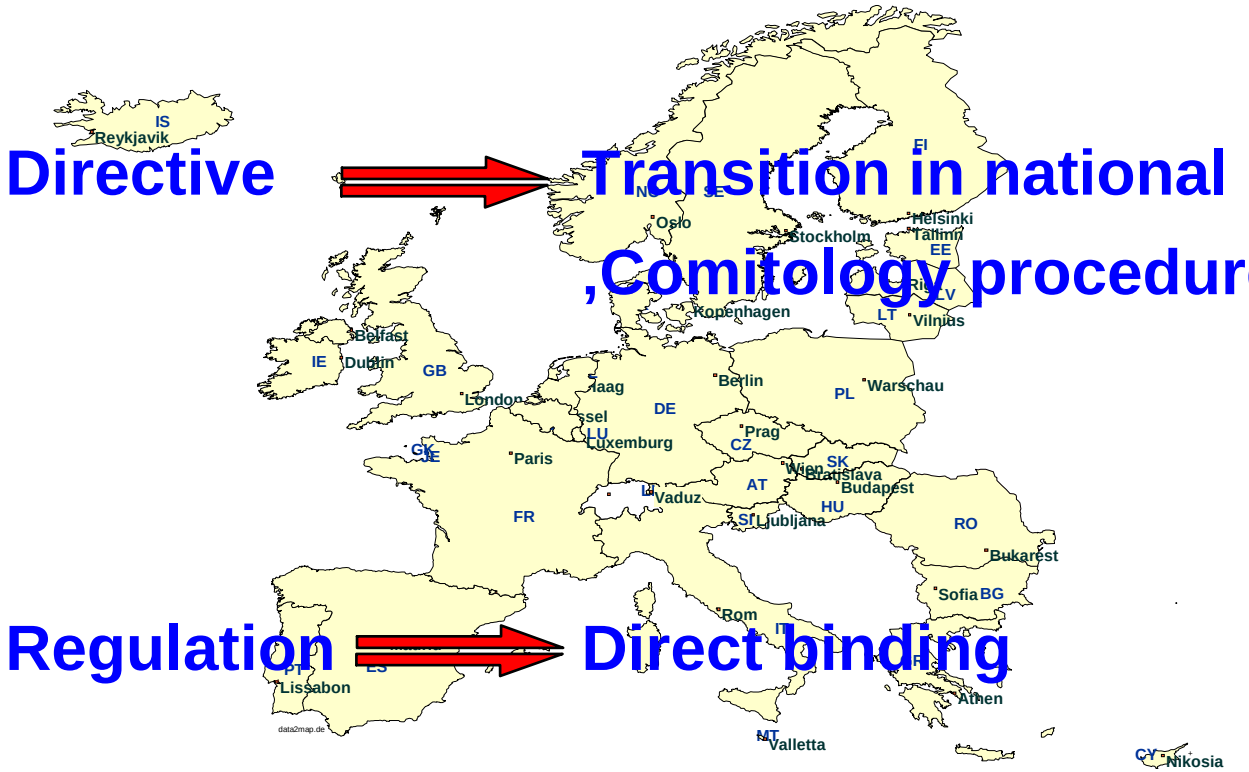
Birka Lehmann

# Clinical Trials

## Directive for Clinical Trials

→ The EU Clinical Trials Directive – legal background

# European Regulation, Directives, Guidance, Guidelines




**Directive** → **Transition in national law**

**‚Comitology procedure‘**

**Regulation** → **Direct binding**

# European Regulation, Directives (Guidelines)

## The role of the EU Commission, Council and European Parliament

**EU-Commission** (Executive)

**27 Commissioner**

**26 Directorate-General**

**Council of the European Union**

**27 Member States**

- **Agreement/approval for regulations/directives**

= co-decision process

**European Parliament**

**http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/links.htm**

# Clinical Trials in Europe – Legal Basis

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

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

COMMISSION DIRECTIVE 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products

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

# Clinical Trials in Europe – Legal Basis

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

# Objectives for new legislation

Protection of subjects participating in clinical trials

Information on clinical trials – including database

Single decision by competent authorities

Single decision by Ethics Committees

Good Manufacturing Practice (GMP)

Good Clinical Practice (GCP)

# Scope

→ Medicinal products including cell and gene therapies

→ All trials:

Phases I to IV including bioavailability/bioequivalence;

National (one or more centres) or multistates;

With or without direct benefit

→ except NON INTERVENTIONAL

→ All populations but special requirements for children and incapacitated adults not able to give their consent

# Directive 2001/20/EC

| | | |
|---|---|---|
| Article 1 | | Good clinical practice new → Directive(Guideline) |
| Article 2 | | Definitions |
| Article 3 | → | Protection of clinical trials subject |
| Article 4 | | Clinical Trials on minors |
| Article 5 | | Clinical Trials on incapacitated adults not able to give informed legal consent |
| Articles 6 – 8 | → | Ethics Committee → guidance |
| Article 9 | → | Competent authorities → guidance |
| Article 10 | | Protocol modification |
| Article 11 | | Eudract database, Exchanges of information → guidance |

# Directive 2001/20/EC

| | |
|---|---|
| Article 12 | Suspension / infringements |
| Article 13 | Manufacture and import of Investigational Medicinal Products → new Directive (Guideline) |
| Article 14 | Labelling |
| Article 15 | Inspections (Inspection procedure, Qualification of inspector) and Master file on the trial and archiving → new Directive (Guideline) |
| Article 16 –18 | Adverse Reactions → guidance |
| Article 17 | Eudravigilance database → guidance |
| Article 19 | General Provisions |

# Follow-up procedures

→ Detailed Guidelines

with comitology procedure adoption by Standing Committee
(Article 21 Directive 2001/20/EC)

→ Detailed Guidance

without comitology procedure – without Standing Committee

→ Publication: by the Commission

# Comitology Procedure

Detailed Guidelines prepared and published by the Commission

→ Article 1
Good Clinical Practice principles

→ Article 13.1
Manufacturing/importation authorisation
requirements for investigational medicinal products

→ Article 15.5
Trial master file, archiving of data
Qualification of inspectors
Inspection procedures

# Without Standing Committee

Detailed Guidance prepared and published by the Commission:

→ Article 8 Submission to Ethic Committee

→ Article 9.8 Submission to Competent Authority

→ Article 11.3 European Database and exchange of information

→ Article 18 Adverse events/reactions reporting

# Clinical Trials in Europe

Detailed Guidance prepared and published by the Commission

- Guidance on application to
  - Competent Authorities
  - Ethics Committees
- Guidance on collection and reporting of SUSARs (Suspected Unexpected Serious Adverse Reactions in clinical trials)
- Guidance on the EudraVigilance database (containing post-marketing ICSRs (Individual Case Safety Reports) and SUSARs)
- Guidance on the EudraCT Database (covering all clinical trials conducted within the Community, to be used by authorities)
- Guideline on the data fields from the EudraCT database that may be included in the EudraPharm database (under development)

(REGULATION (EC) No 726/2004 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL)

# Comitology Procedure = Commission Directive

→ Article 1
Good Clinical Practice principles

→ Article 13.1
Manufacturing/importation authorisation
requirements for investigational medicinal products

→ Article 15.5
Trial master file, archiving of data
Qualification of inspectors
Inspection procedures

# Clinical Trials in Europe – Legal Basis

COMMISSION DIRECTIVE 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products

## Consultation phase
## (July 2002 – October 2002)

→ Comments from Pharmaceutical Industry/companies

→ Comments from Research organisations

→ Comments from Member States

# Directive 2005/28/EC

**Chapter 1** **Scope**

Set out provisions for non-commercial trials → Guidance

**Chapter 2** **Good Clinical Practice**

Good Clincial Practice – Principles & details
Ethics Committees
Sponsor
Investigator‘s Broschure

**Chapter 3** **Manufacturing and import authorisation for investigational medicinal products**

Requirements
‘Exceptions’
Time-lines for the competent authorities

# Directive 2005/28/EC

**Chapter 4** **Documentation constituting the Trial Master File and archiving**

Retention requirements
Retention times
Ownership of data

**Chapter 5** **Qualification of the Good Clinical Practice Inspectors**

Education
Knowledge
‚independcy‘

**Chapter 6** **Good Clinical Practice Inspections Procedures**

Networking of Member States and EMEA
Guidance documents
Records keeping (data base)

# Compilation of all documents relating to clinical trials:

# Volume 10 (EudraLex)

**Chapter I** **Application and Application Form**

- Guidance on application to Competent Authorities and to Ethics Committees
- Guidance on the **EUDRACT** Database (covering all clinical trials conducted within the Community, to be used by authorities)

**Chapter II** **Monitoring/Clinical Safety**

- Guidance on collection and reporting of SUSARs (Suspected Unexpected Serious Adverse Reactions in clinical trials)
- Guidance on the **Eudravigilance** database (containing post-marketing ICSRs (Individual Case Safety Reports) and SUSARs)

http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev10.htm

**Chapter III Information on the quality of the Investigational medicinal product**

- Annex 13 (Good Manufacturing Practice)
- Community basic format for manufacturing authorisation/manufacuters/importers
- CHMP/EMEA Guideline for the quality of Investigational Medicinal Products

**Chapter IV Recommendation on inspections**

- Recommendation on the qualifications of inspectors
- Recommendation on inspection procedures

**Chapter V Additional Information**

- Recommendation on the documentation constituting the Trial Master File and on archiving
- Questions and Answers Document
- CHMP/ICH/135/95 Note for Guidance on Good Clinical Practice

**Chapter VI Legislation**

- Directive 2001/20/EC… on… Clinical Trials…
- Directive 2003/94/EC Good Manufacturing Practice
- Directive 2005/28/EC on Good Clinical Practice

# Goal reached?

## Harmonisation of:

- Time-line for opinion by Ethics Committees
- Time-line for authorisation by competent authorities
- Application form (including EudraCT-No)

  → Increased data requirements and application details compared to old system → but unified format and contents of application

- Reporting for AE/AR/SUSARs

  → Pharmacovigilance reporting system → selective approaches pointed out in guidance documents

- Medicinal Product in accordance with Good Manufacturing Process → Patient need assurance of high quality of medicinal product

  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

# Main challenges

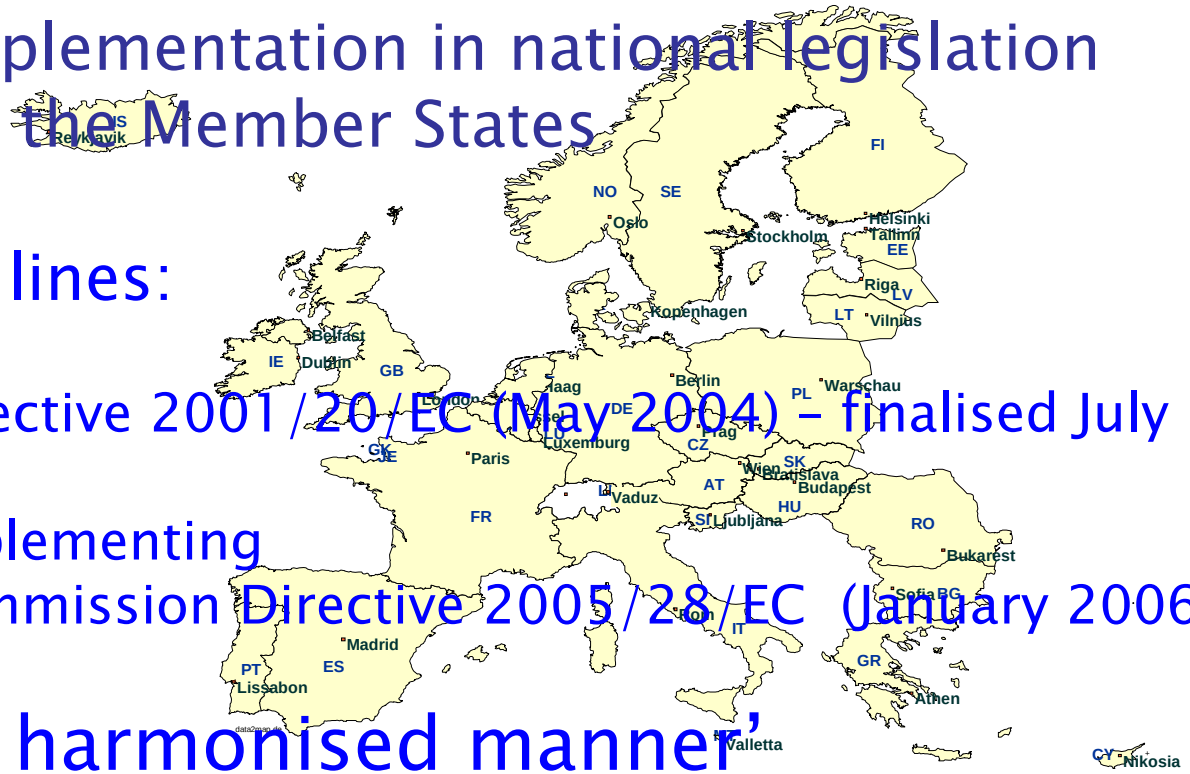
- Implementation in national legislation by the Member States

Time lines:

- Directive 2001/20/EC (May 2004) – finalised July 2006

- Implementing Commission Directive 2005/28/EC (January 2006) – on-going

‘in a harmonised manner’



# Clinical Trials in Europe

Single Ethics Committee opinion

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local Ethics Committee and ‚leading' Ethics Committees


Ethics Committee
And
Competent Authority

in each Member State

# Network Competent Authorities

- Heads of Agencies: Clinical Trials Facilitation Group (Competent Authorities)
  - Platform for the ex-change of information and development harmonised standards for the evaluation of clinical trials
- Ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use

  Development of
  - harmonised dossier requirements and application form
  - definitions, questions and answers on specific topics
- GMP/GCP Inspectors Group (Coordination by EMEA)
  - Development/definitions in the frame of inspections and alerts in clinical trials

- **Guideline on the data fields from the European clinical trials database (EudraCT) that may be included in the European database on Medicinal Products**
  **EudraPharm** Regulation (EC) No. 726/2004, Article 57.1 (l) and
  Article 57.2 – only for medicinal products with a Marketing Authorisation

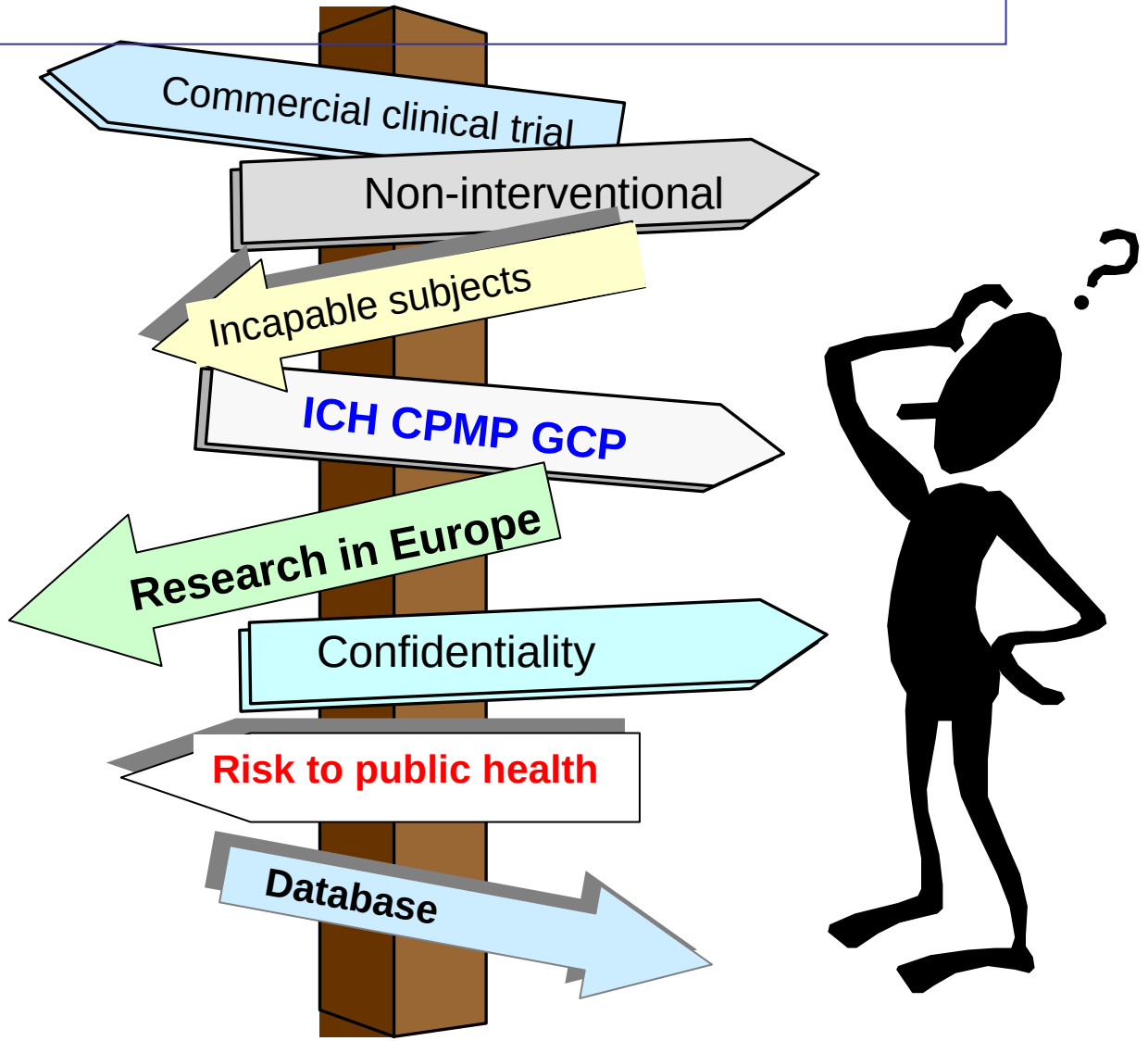
- **Guidance** on 'specific modalities' for non-commercial trials referred to in the Commission Directive 2005/28/EC
  laying down the principles and detailed guidelines for good clinical practice.
  *Will be included in **Chapter V Additional Information***

- **Definition** of
  - Investigational medicinal product
  - Non-investigational medicinal product

  *Will be included in **Chapter V Additional Information***
  *in Questions and Answers Document*

  Were published for consultation.
  Discussion with Member States after public consultation for final publication

# Further development needed?



Enterprise and Industry

http://ec.europa.eu/enterprise/pharmaceuticals/index_en.htm

26/02/2007 Pharmaceutical Committee

Summary record of the 61th meeting, 5 December 2006

## Clinical Trials Directive

- The Commission representatives presented a report on the activities of the '*Ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use*' concerning the implementation of the legislation in the Member States and the guidance prepared since the establishment of the Ad hoc group in 2001.
- The report stated that it is not yet possible to fully assess the impact of the guidance prepared and concluded that some difficulties as regards the administrative procedures and differences in implementation are not overcome yet.
- Finally, it has identified the priority areas which require future attention, in particular those
  - → related to approval times and procedures,
  - → specific national requirements,
  - → the definition of investigational medicinal product,
  - → the conduct of non-commercial clinical trials and
  - → the functioning and coordination with competent authorities of the activities of ethics committees.
- The Committee endorsed these working priorities concerning the implementation of the Clinical Trials Directive and supported the orientation for the Ad Hoc Group to focus on these priorities.

# Amendments?

# future?

# New legislation?

# Clinical Trials

## Directive for Clinical Trials

→ The EU Clinical Trials Directive – legal background


Thank you for your attention