Clinical Trials Directive (2001/20/EC) – Implementation in the EU - Member States

Prof. Dr. Barbara Sickmüller,
Bundesverband der Pharmazeutischen Industrie (BPI)
Member of EFPIA STR-Policy Committee
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Topics

- Review of implementing texts supporting the Directive
- Status of implementation in Member States (MSs) – Overview by EFPIA (May 2004)
- Major issues identified with the implementation of the clinical trials directive in MSs
- Opportunities

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Review of implementing texts supporting the Directive

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Review of the finalized implementing texts supporting the Directive: 2 Types - Legal differences

Guidelines which are legally binding for implementation by MS

- Texts requiring « Standing Committee » approval
  - ➢ « Committology Procedure »

Guidance documents which are not legally binding

- Usual guidance documents, without Standing Committee
  - ➢ changes are easier to adopt

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2 Types of implementing texts
Legal differences

Guidelines (binding for implementation in MSs)

- GCP principles Manufacturing/importation authorisation requirements of an IMP (Com. Dir. expected)
- Manufacturing and labelling of IMPs (Annex 13 of GMP guide) – published
- Inspections: Qualifications of inspectors and Inspection procedures for the Verification of GCPCompliance – expected
- Documentation relating to the trial (Trial Master File and Archiving) – expected

Guidances not binding / rev. published (April 2004)

- ADR reporting (SUSAR-Suspected Unexpected Serious Adverse Reaction) and annual reports
- ADR Data Base: Eudravigilance - Clinical Trial Module
- Clinical Trial Data Base (EUDRACT) - working
- Application format to be submitted to Ethics Committees
- Application format to be submitted to competent authorities (incl. notification of substantial amendments and declaration of end of trial)

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Development of a new CPMP Guideline on Quality (EMEA, 22 April 2004)

- CPMP Guideline on the quality part of a request for authorisation of a clinical trial will be developed
- MSs have developed different requirements for the quality part
- For multi-centre clinical trials it is important to harmonise these requirements through the EU
  - Requirements for phases I to III
  - Differentiation between clinical trials and marketing authorisation
  - Chapter for modified/manipulated comparator products
  - Radio-active/radio-labelled substances
  - Requirements for herbal medicinal products
- Draft guideline to be released by EMEA in November (6 months consultation)

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Status of implementation in MSs - Overview

(Result of an EFPIA Questionnaire, May 2004)

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Directive 2001/20/EC: Status of implementation in MSs (1)

(Result of an EFPIA Questionnaire, May 2004)

- **Austria**
  - Law adopted: 29. April 2004 (35. Bundesgesetz zur Änderung u. a. des AMG hinsichtlich der klinischen Prüfung)
  - Date of implementation: 01. May 2004
- **Belgium**
  - Law adopted: 29 April 2004
  - Date of implementation: 01 May 2004
- **Denmark**
  - Law adopted
  - an Executive Order will be issued containing details
  - will come into force on 1 May 2004
- **France**
  - 2nd reading by Senate in June
  - final adoption planned for 01 July
  - Implementation decrees necessary
  - Implementation announced for end of 2004/early 2005
  - Transitory measures have been put in place

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Directive 2001/20/EC: Status of implementation in MSs (2)

- **Germany (1)**
  - Legislation not finalised
  - Conciliation procedure between the two houses (Parliament and Bundesrat)
  - Implementation degrees and guidelines are discussed in parallel
  - Competent authority:
    - Implicit (30 days) / explicit procedure 30/60 days, e. g. for all biotech (30) and other products with active ingredients derived from human or animal origin products (60)
    - Phase I, 30 days, as part of a group of studies: 14 days
    - Somatic celltherapy, genetherapy, GMOs 90 days, max. 180 days;
    - xenogene celltherapy no timelines are defined

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Directive 2001/20/EC: Status of implementation in MSs (3)

- **Germany (2)**
  - Ethics Committees procedure
    - Coordinating EC but information has to be send by sponsor in addition to all afflicted local ECs
    - Local ECs primarily to assess suitability of the investigator and quality of the facilities
  - Timelines for Ethics Committees:
    - Multi-centre: 60 days, mono-centre 30 days
    - Phase I, 30 days; as part of a group of studies: usually 14 days
    - Somatic celltherapy, GMOs 90 days, max. 180 days;
    - Genetherapy 180 days
    - xenogene celltherapy no timelines are defined

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Directive 2001/20/EC: Status of implementation in MSs (4)

- **Germany (3)**
  - –Inspections for supplies from third countries will not be required routinely
  - –Date for implementation: 01 July / 01 August?
  - –Transitional measures are defined in the law
    - Clinical trials where the application to the EC through the „Leiter der klinischen Prüfung“ has been done before the date of implementation, the current law will be applicable
    - ADR reporting: compliance with new law

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Directive 2001/20/EC: Status of implementation in MSs (5)

(Result of an EFPIA Questionnaire, May 2004)

- **Greece**
  - Legislation finalized: 31 December 2003
  - Implementation: in theory 01 May 2004
  - practical implementation possible from 01 June 2004

- **Ireland**
  - Legislation finalised 30 April 2004
  - Date of implementation: 01 May 2004
  - Delay expected while ECs are accredited under new legislation
  - Trials approved prior will continue to be regulated under old legislation

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Directive 2001/20/EC: Status of implementation in MSs (6)

(Result of an EFPIA Questionnaire, May 2004)

- **Italy**
  - Legislation adopted on 09 August 2003
  - Date of implementation: 01 January 2004
  - Implementation degrees are still in discussion
- **Netherlands**
  - Legislation not finalized
  - Date of implementation: Earliest 01 July 2004
- **Norway**
  - Legislation adopted
  - Date of implementation: 01 May 2004
  - EC Responsibility still needs compliance with Directive

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Directive 2001/20/EC: Status of implementation in MSs (7)

(Result of an EFPIA Questionnaire, May 2004)

- **Portugal**
  - Legislation not finalised
  - Implementation: open
- **Spain**
  - Legislation partially adopted
  - Partial entry into force on 01 May 2004
  - final implementation when relevant EU guidelines and national implementation guide finalised
- **Sweden**
  - Final legislation adopted June 2003
  - Entry into force on 01. May 2004
- **UK**
  - Legislation finalised on 01 May 2004
  - Implementation in the way

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Major issues identified with the implementation of the clinical trials directive

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Transitional arrangements

- **National Transposition in MS**
  - –no consistent process nor timing across all MSs with regard to ECs and CAs
- **EUDRACT is working**
  - –number only required for studies starting after May 1, 2004, or later
  - –depending on national implementation
- **Procedures for amendments for already started Clinical Studies**
  - –no consistent approach

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Lack of Consistency of interpretation of provisions, requirements and definitions

- **Simple definitions interpreted differently**
  - IMP (investigational medicinal product)
  - Non-interventional studies
  - sponsor
- **Application to competent authorities**
  - Notification or Authorisation
- **Data requirements for Phase I studies**
- **Ethics Committees Procedure and single opinion**
  - Different procedures in MSs
- **Structure of the Investigational Product Annual Report - IPAR**
  - Different schedules for submission dependent on MS
- **Delegation of competent authorities role to Ethics Committees**
  - impact on intellectual property (i. e. Italy)

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Process issues

Further guidance is missing

- **Business process required for submission of amendments**
- **First time in man studies**
- **Definition of a valid application**
- **GMP aspects**
  - Once site approved by product type then each IMP does not need approval
  - Issues with certain countries (e.g. Sweden) for third country manufacturing site inspections

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ADR – Reporting (Phase IV Clinical Trials)

- **Germany**
  - –Reporting **SUSARs**
  - –In addition MAH should report to the competent authorities **all suspected serious** adverse reactions, which occur in clinical trials with maketed products within 15 days,
  - –SUSARs are collated in EudraVigilance - Clinical Trial Modul
  - –All other suspected serious ADRs will be collated in the EudraVigilance Database?

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Opportunities

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Opportunities (1)

- First step to more harmonisation in the area of clinical trials (CT) in EU 25
  - –Better Harmonisation of application formats to be submitted to Ethics Committees (EC) and to competent authorities (CA)
  - –Quality of IMP: Harmonisation will be further worked on (CPMP/EMEA)
- Shorter time frame for early development in phase I studies
- Training and accreditation of EC in some MS (maybe necessary in other MSs)
- Clearer separation of EC vs. CA responsibilities

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Opportunities (2)

- EU – Commission
  - –After implementation it is necessary to further improve and harmonise rules on CT
  - –On basis of experience
- Heads of Agencies
  - –Have set up a „Clinical Trials Coordination Group“
  - –Harmonisation of requirements
- Possibility for a mutual recognition of CT applications in future?
- Faster approval procedure with less problems because CA „know“ the product already?

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