

# International Clinical Trials: Current Issues in Clinical Trial Regulation and Future Reforms: EU, US, and Beyond: a European perspective

International Pharmaceutical Regulatory and Compliance Congress and Best Practices Forum

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# Overview

1. Background : current legal framework
2. What aspects of the implementation of the Directive 2001/20/EC do not work well ?
3. Compliance issues

# 1. Background

- The Directive 2001/20/EC relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

# 1. Background: Context

- Harmonisation of the provisions governing the conduct of clinical trials in the EU
- Choice of the Directive as a legal tool :
  - Mandatory implementation in every Member States
  - Flexibility as to the means
- Legal background :
  - The World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects 1964
  - Internal Conference of Harmonisation (ICH) guidelines and good clinical practice guidelines drafted by the European Commission

# 1. Background: Scope of the Directive

- Interventional clinical trials of medicinal products in the EU
- Compliance with Good Clinical Practice (“GCP”) and Good Manufacturing Practice (“GMP”)
- Definition of tasks, responsibilities and legal entities
- Timelines and administrative processes
- Improvements in the quality of research and the protection of patients

# 1. Background: Protection of clinical trial subjects (Art. 3)

- Risk-benefit balance for the subjects
- Positive opinion from the Ethics Committee and/or competent authority
- Written consent revocable at any moment
- Mandatory insurance or indemnity to cover the liability of the investigator and sponsor
- Specific provisions for minors and incapacitated adults (art. 4 and 5)

# 1. Background: Ethics Committee (Art. 6)

- Any clinical trials on human beings must be subject to an opinion issued by an Ethics committee before the start of the trial
- Reasoned Opinion must be issued within 60 days
- Adoption of a single opinion for multi-centre clinical trials taking place in a single Member State
- Adoption of a single opinion for each Member State in case of multi-centre clinical trials carried out simultaneously in several Member States

# 1. Background: Competent Authority (Art.9)

- The sponsor must apply for approval to the competent authority before any experiments on human beings take place
- In case the sponsor is informed of grounds for non-acceptance, he may - on one occasion only - amend the content of the request, taking account of the grounds given
- If the sponsor fails to amend the request accordingly, the request shall be deemed rejected
- Authorisation is granted within a max. of 60 days
- Written authorisation may be required for trials on medicinal products which do not have a MA or which have special characteristics (for ex. which contain biological products), and for trials involving products for gene therapy or containing GMO



# 1. Background: Sponsor of a clinical trial

- The sponsor can be an individual, a company, an institution or an organisation (Art.2)
- The sponsor or his legal representative (only one in one clinical trial) must be established in the EU
- If the sponsor is not located in the EU, the legal representative should be responsible for the civil and criminal liability of the sponsor (art. 19)
- The sponsor and the investigator may be the same person
- The sponsor may delegate any or all of his trial-related tasks/duties and functions. However, the sponsor remains ultimately responsible of the compliance of the course of the trial with the Directive
- Investigational medicinal products and if need be the devices used for their administration are made available free of charge by the sponsor

# 1. Background: Exchange of information (Art.11)

- Creation of a European database for clinical trials (EudraCT) in 2004, accessible only to the Competent Authorities, the EMEA and the Commission
- Register of all clinical trials in the EU:
  - Overview of all clinical trials in the EU
  - Identification of ongoing, completed or terminated clinical trials
  - Provision of information on the GCP and clinical trial related GMP inspections undertaken by the competent authorities
  - Report of all adverse serious adverse reaction
  - Notification to all competent authorities when a trial is terminated for safety reasons

# 1. Background: Suspension of the trial or infringements (Art.12)

- Possible suspension or prohibition of the trial by the Member State if:
  - Suspicion that the conditions in the request for authorisation are no longer met, or
  - Doubts about the safety or scientific validity of the clinical trial
- Before the Member State reaches a decision of suspension/prohibition, the sponsor and/or investigator must be asked for their opinion, to be delivered within one week

# 1. Background: Manufacture and import of investigational medicinal products (Art.13)

- Subject to the holding of authorisation
- The holder of the authorisation has permanently and continuously at his disposal a qualified person
- The qualified person must :
  - certify that each batch of the medicinal product has been manufactured in compliance with GMPs
  - keep up to date a register as operations are carried out
- The Commission has published guidelines laying down adapted provisions relating to labelling for investigational medicinal products intended for clinical trials

# 1. Background: Verification of compliance of investigational medicinal products with GCPs and GMPs (Art. 15)

- Inspection of the sites concerned by any clinical trial conducted
- Conducted by the Competent Authority of the Member State concerned, which shall inform the EMEA
- Coordination by the EMEA
- An inspection report is established at the end of the inspection, and must be made available to the sponsor while safeguarding confidential aspects

# 1. Background: Notification of adverse events (Art. 16)

- The investigator shall report all serious adverse events immediately to the sponsor except when stated otherwise in the protocol
- The immediate report must be followed by detailed, written reports, which must identify subjects by unique code numbers assigned to the latter
- The sponsor shall keep detailed records of all adverse events which are reported to him by the investigator

# 1. Background: Notification of serious adverse reactions (Art. 17)

- The sponsor must notify the Competent Authority and Ethics Committee of any suspected serious unexpected adverse reaction
- This notification must be made immediately and, at the latest within 7 days from the day the sponsor became aware of effects which caused the death or endangered the life of the person (or within 15 days in other cases)
- The sponsor shall also inform all investigators
- Once a year throughout the clinical trial, the sponsor shall provide the Member State and the Ethics Committee concerned with a listing of all suspected serious adverse reactions which have occurred over this period

# 1. Background: A comparative focus – Implementation of the Directive in France and in the UK

- Timescales :
  - Assessment period before the Competent Authority : 60 days in France, 30 days in the UK
  - Assessment period before the Ethics Committee : 35 days in France, 60 days in the UK
- Appeals against the opinion of the Ethics Committee :
  - France : the sponsor can refer the matter to the Health Minister within 15 days of the negative opinion and said Minister can appoint another Ethics Committee
  - UK : the investigator can appeal before the UK Ethics Committee within 90 days
- Specific categories of volunteers
  - Pregnant women : Nothing in the Directive. They are specifically considered under French Law. No specific provision under UK Law
  - Minors : French Law prohibits trials on minors if they refuse or withdraw their consent. The Directive and English Law provide that such refusals or withdrawals shall be simply “considered”.



## 2. What aspects of the implementation of the Directive do not work well?

- Directive 2001/20/EC and accompanying guidances provide a harmonized legal framework.
- Nevertheless, its implementation and interpretation creates discrepancies
- Transparency

## 2. What aspects of the implementation of the Directive do not work well?

- Interventional and non-interventional trials
  - Definition of « clinical trial » (art. 2 (a)) :

*« Clinical trial : any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy. »*

## 2. What aspects of the implementation of the Directive do not work well?

- Interventional and non-interventional trials

« Non-interventional trials » are not within the scope of the Directive

- Definition of « non-interventional trials » (art. 2 (c)) :

*« non-interventional trial : a study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data »*

## 2. What aspects of the implementation of the Directive do not work well?

- Interventional and non-interventional trials
  - Divergent interpretation at Member State level :
    - the meaning of « intervention » is different in some Member States.

In some countries, post-marketing trials are considered as non-interventional ones and in some others, they are considered as interventional ones.
    - need to create an intermediate category: low risk intervention without need of authorization by competent authority but only by Ethics committees
  - Need to revise definitions

## 2. What aspects of the implementation of the Directive do not work well?

- Commercial and non-commercial trials and sponsors
  - Different GCP standards for commercial trials and for non-commercial trials
    - perception of two levels of quality in the legislation and its implementation
    - trials conducted by non-commercial sponsors should be admissible for MA application purposes
  - The cost for implementing the legislation and its administrative procedures has led to a reduction of the number of independent trials
  - Need for improvement of the cost-effectiveness of non-commercial trials without reducing GCP compliance

## 2. What aspects of the implementation of the Directive do not work well?

- Transparency
  - Access to the EU clinical-trials database (EudraCT) only for NCAs, the European Commission and the EMEA
  - Data on ongoing trials conducted in adults prior to a MAA is confidential :
    - it does not allow the public/patients to find a clinical trial to participate in,
    - nor to obtain information on the main outcomes of performed trials
  - Need for completing the implementation of publication of data from EudraCT

## 2. What aspects of the implementation of the Directive do not work well?

- No uniform application dossier for authorization of a clinical trial:
  - insufficient harmonization of administrative processes
  - duplication of assessments
- Variation in safety reporting
  - lack of harmonization
- No uniform interpretation on «*substantial amendments* »

## 2. What aspects of the implementation of the Directive do not work well?

- Proposal of remedies made by the industry:
  - have a single and unique clinical trial application dossier ;
  - apply strictly current report requirements in accordance with Detailed Guidance on the collection, verification and presentation of adverse reaction reports (ENTR/CT3 April 2006) ;
  - provide definition of « *substantial amendment* ».
  - some stakeholders even propose the adoption of a EU Regulation to replace the Directive



### 3. Compliance issues

- Good Clinical Practice (« GCP »)
- Patients' financial remuneration or compensation
- Anti-kickback rules
- Information / Advertising issues

# 3. Compliance issues

## ■ Good Clinical Practice (“GCP”)

### Key-Documents

- 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 and requirements for authorisation of the manufacturing or importation of such products
- “European guidance on Good Clinical Practice CPMP/ICH/135/95” (last revision 1996)
- “European guidance on the content of the trial master file and archiving” (July 2006)
- Awaited document : European guidance on “specific modalities” for non-commercial trials

## 3. Compliance issues

- Good Clinical Practice (“GCP”)

The GCP guidelines set out ethical principles applying to :

- the design, conduct, recording and reporting of clinical trials
- the manufacturing or import authorisation
- the inspection procedures

# 3. Compliance issues

- Good Clinical Practice (“GCP”)

Perspective for the future :

- Consensus on the need for a single set of GCP standards for commercial and non-commercial trials  
→ However, specific additional guidance on non-commercial trials are awaited: stakeholders expect improvements concerning the cost-effectiveness of non-commercial trials
- Review of Directives 2001/20/EC and 2005/28/EC should formerly require similar ethical GCP standards for trials performed outside the EU.  
→ avoidance of clinical-trial dumping

## 3. Compliance issues

- Patients' Financial remuneration or compensation

### **Article 6 of Directive 2001/20/EC :**

*« In preparing its opinion, the Ethics Committee shall consider (...) the amounts and, where appropriate, the arrangements for rewarding or compensating investigators and trial subjects (...) »*

### **Article 4(d) of Directive 2001/20/EC :**

*For clinical trials on minors « (...) no incentives or financial inducements are given except compensation »*

### **Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee (February 2006) :**

*This guidance highlights that the applicant must set out “the amount and procedure of remuneration or compensation of subjects (description of amount paid during the participation in the trial and for what, i.e. travel cost, loss of earning, pain and discomfort etc)”.*

## 3. Compliance issues

- Patients' Financial remuneration or compensation

Example of the French implementing provision

Article L. 1121-11 of the French Public Health Code only authorizes compensation for the expenditures

This compensation cannot exceed 4500 euros for each person for a global 12 month period (Decree (“arrêté”) of April 25, 2006)

## 3. Compliance issues

- Anti-kickback issues

In addition to the clinical trial provisions, the stakeholders (companies/ healthcare professionals) must comply with the European and National anti-kickback provisions

## 3. Compliance issues

- Anti-kickback issues

→ European perspective

Article 14 of the EFPIA Code (European Federation of Pharmaceutical Industries and Associations) authorizes remuneration of healthcare professionals for participating in clinical trials provided notably :

- a written contract is agreed in advance
- the criteria for selecting the physicians are directly related to the identified need
- the hiring of the healthcare professional is not an inducement to recommend, prescribe, purchase, supply, sell or administer a particular medicinal product



## 3. Compliance issues

- Anti-kickback issues

→ European perspective

According to Article 14.02 of the EFPIA Code, the contract shall include provisions regarding the obligation of the consultant to declare its relationship with a company whenever he/she writes or speaks in public

## 3. Compliance issues

- Anti-kickback issues

→ French perspective

French similar provision : Article L. 4113-6 of the French Public Health Code

In France, contravening companies/physicians are exposed to criminal sanctions :

- doctors are exposed to a fine of 75,000 euros and a 2-year imprisonment
- companies are exposed to a fine of 375,000 euros

## 3. Compliance issues

- Advertising / Information issues

**Specific vigilance as regards national and European provisions on :**

- promotion of medicinal products e.g. pre-approval pharmaceutical products, including results of clinical trials, cannot be used for promotion

- Ethical issued by the national Medical Doctor Societies in relation to the recruiting of patients.

In France, you cannot pay healthcare professionals to « suggest » their patients to participate in clinical trials.

This is what could be done in the short period of time allowed.  
Thank you for your indulgence and for your attention and many thanks to  
my team.

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