



Agenzia Italiana del Farmaco



***The Italian Legislation and the work of
the Italian Medicines Agency (AIFA) in
the field of ethics of Clinical Trials***

Umberto Filibeck

AIFA

Head of GCP Inspectorate and GCP Promotion Unit

**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**

**Transposed in the Italian Legislation by the Legislative
Decree 24 June 2004, n. 211**

**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

Transposed in the Italian Legislation by the Legislative Decree 6 November 2007, n. 200

MAIN PROVISIONS

- **All clinical trials, including bioavailability and bioequivalence studies, shall be designed, conducted and reported in accordance with the principles of good clinical practice.**

ICH-CGP PRINCIPLES

A) ETHIC GUARANTEE

2.1 Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(S).

2.3 The rights, safety, and well-being of trial subjects are the most important considerations and should prevail over interests of science and society.

2.6 A trial should be conducted in compliance with the protocol that has received prior EC approval.

2.9 Freely given informed consent should be obtained from every ⁵ subject prior to clinical trial participation.

B) TECHNICAL-SCIENTIFIC GUARANTEE

2.4 The available nonclinical and clinical **information** on an investigational product **should be adequate** to support the proposed clinical trial.

2.7 The **medical care given** to, and medical decisions made on behalf of, subjects should always be the responsibility of a **qualified physician** or, when appropriate, of a qualified dentist.

2.8 Each individual involved in conducting a trial should be **qualified by education, training, and experience** to perform his or her respective task(s).

2.12 **Investigational products** should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (**GMP**). They should be used in accordance with the approved protocol.

C) PROCEDURAL GUARANTEE

2.10 All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

2.11 The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement.

2.13 System with procedures that assure the quality of every aspect of the trial should be implemented

A Clinical Trial may be undertaken only if, in particular, besides what foreseen by GCP principles:

- The rights of the subject to physical and mental integrity, to privacy and to the protection of the data concerning him, are safeguarded.
- The subject may without any resulting detriment withdraw from the clinical trial at any time by revoking his informed consent.
- Provision has been made for insurance or indemnity to cover the liability of the investigator and sponsor.
- The subject shall be provided with a contact point where he may obtain further information.
- No incentive or financial inducement are given.

A Clinical Trial on minors may be undertaken only if:

- The informed consent of the parents or legal representative has been obtained; consent must represent the minor's presumed will and may be revoked at any time, without detriment to the minor.
- The minor has received information according to its capacity of understanding, from staff with experience with minors, regarding the trial, the risks and the benefits.
- The Ethics Committee, with paediatric expertise or after taking advice in clinical, ethical and psychosocial problems in the field of paediatrics, has endorsed the protocol.

ETHICS COMMITTEE

'Ethics committee': an independent body in a Member State, consisting of healthcare professionals and non-medical members, whose responsibility it is to protect the rights, safety and wellbeing of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent;

ETHICS COMMITTEE

- The Ethics Committee shall give its opinion, before a clinical trial commences.
- In preparing its opinion, the Ethics Committee shall consider, among others:
 - (a) the relevance of the clinical trial and the trial design;
 - (b) whether the evaluation of the anticipated benefits and risks is satisfactory and whether the conclusions are justified;
 - (c) the protocol;
 - (d) the suitability of the investigator and supporting staff;
 - (e) the investigator's brochure;
 - (f) the quality of the facilities;
 - (g) the adequacy and completeness of the written information to be given and the procedure to be followed for the purpose of obtaining informed consent;
 - (h) any insurance and provision for indemnity or compensation in the event of injury or death attributable to a clinical trial;
 - (i) the amounts and, where appropriate, the arrangements for rewarding or compensating investigators and trial subjects;
 - (j) the arrangements for the recruitment of subjects.

COMMENCEMENT OF A CLINICAL TRIAL

- EC approval
- Competent Authority authorization
- It is necessary written authorization by Italian Competent Authorities, for all Phase I CTs and for all CTs involving medicinal products for gene therapy and somatic cell therapy. No gene therapy trials may be carried out which result in modifications to the subject's germ line genetic identity.

AMENDMENTS

- Amendments may be made to the conduct of a clinical trial following the same procedures for CT authorization.

SUSPENSION/WITHDRAWAL OF THE CLINICAL TRIAL/MARKETING AUTHORIZATION

- When AIFA has information raising doubts about the safety or scientific validity of the clinical trial, it may suspend or prohibit the clinical trial.
- Withdrawal of MA when CT have been conducted not in compliance with GCP
- Refusal of MA application based on CT performed in EU and extra-EU Countries not in compliance with GCP ethical principles.

MANUFACTURE AND IMPORT OF INVESTIGATIONAL MEDICINAL PRODUCTS (IMP)

- Manufacture or importation of IMP must be authorized by AIFA

VERIFICATION OF COMPLIANCE OF CLINICAL TRIALS AND INVESTIGATIONAL MEDICINAL PRODUCTS WITH GOOD CLINICAL AND MANUFACTURING PRACTICE

- To verify compliance with the provisions on good clinical and manufacturing practice, AIFA appoints inspectors to inspect the sites concerned by any clinical trial conducted, particularly the trial site or sites, the manufacturing site of the investigational medicinal product, any laboratory used for analyses in the clinical trial and/or the sponsor's premises and ethics committee as well.
- The inspections shall be conducted on behalf of European Community and the results shall be recognised by all EU Member States.

VERIFICATION OF COMPLIANCE OF CLINICAL TRIALS AND INVESTIGATIONAL MEDICINAL PRODUCTS WITH GOOD CLINICAL AND MANUFACTURING PRACTICE

- Good clinical practice inspections may take place on any of the following occasions:
 - (a) before, during or after the conduct of clinical trials;
 - (b) as part of the verification of applications for marketing authorisation;
 - (c) as a follow-up to the granting of authorisation.
- Improvement and harmonisation of inspection guidance shall be achieved by the Member States, in collaboration with the Commission and the Agency, through joint inspections, agreed processes and procedures and sharing of experience and training.

VERIFICATION OF COMPLIANCE OF CLINICAL TRIALS AND INVESTIGATIONAL MEDICINAL PRODUCTS WITH GOOD CLINICAL AND MANUFACTURING PRACTICE

- To verify compliance with the provisions on good clinical practice principles the AIFA GCP Inspectorate may require advice from the Bioethics Italian National Committee established at the Presidency of Council of Ministers

INSPECTION ACTIVITY OF AIFA GCP INSPECTORATE (January 2004 – February 2008)

In situ Inspections

National Inspections and consulting visits: **135**

International, EMEA or joint (with other UE and extra UE inspectorates) Inspections : **21**

Evaluation on documentation about inspection reports from foreign National Authorities regarding bioequivalence studies performed in extra-EU Countries: **67**

Total of above mentioned inspection evaluations: **223**

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INSPECTION ACTIVITY OF AIFA GCP INSPECTORATE (January 2004 – February 2008)

Different kind of inspection activities

In situ inspections **156**

- Trial Sites: 67
- System inspections and consulting visits: 20
- Ethics Committees: 37
- Pharmacies and Laboratories: 32

Evaluation on documentation: **67**

PERMANENT OR ENDURING NEGATIVE OUTCOMES FROM INSPECTIONS

(January 2004 – February 2008)

From the 156 in situ inspections

- 23 MAs refused/suspended/withdrawn or new clinical trials required for lack of GCP compliance/legal requirements or data not reliable
- 16 Suspension of Clinical Trials or Study sites
- 12 Communications to International Scientific Journals when data are published from “non profit” study not reliable
- 2 Communication to public prosecutor

Total of negative outcomes: 53

(NOTE that from the same inspection could arise more than one negative outcome and more than one MA withdrawn etc.)

PERMANENT OR ENDURING NEGATIVE OUTCOMES FROM INSPECTIONS

(January 2004 – February 2008)

Out of 67 evaluations on documentation for extra EU Countries

37 considered not acceptable



37 MAs not granted

SOME EXAMPLES OF UNETHICAL TRIALS AS CAUSE OF SANCTIONS

- Panic syndrome induced by CO₂ in healthy volunteers
- Bronchial asthma induced in allergic population
- False controls of IMP adverse reactions
- IMP not authorized