



EUROPEAN COMMISSION
ENTERPRISE DIRECTORATE-GENERAL

Single market, implementation and legislation for consumer goods
Pharmaceuticals : regulatory framework and market authorisations

Brussels,
ENTR/F/2 D(2002)

**DETAILED GUIDELINES ON INSPECTION PROCEDURES FOR
THE VERIFICATION OF GCP COMPLIANCE**

Comments are expected before 16 September 2002

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INSPECTION PROCEDURES FOR THE VERIFICATION OF GCP COMPLIANCE.

Draft agreed for release for consultation - 12 June 2002

Description of the EU System

Good Clinical Practice (GCP) inspections are performed in order to verify protection of the rights and welfare of trial subjects, compliance with the provisions of GCP and the quality of data generated in clinical trials. To this end, and to fulfil the requirements of Directive 2001/20/EC article 15 and to verify compliance with provisions of Directive 2001/83/EC, annex I part IV, Member States shall appoint inspectors and establish inspection programs within their own territories and may perform inspections in 3rd countries. Inspection reports are made available to the sponsor while safeguarding confidential aspects. The inspection reports may also be made available to the other Member States, to the Ethics Committee and to the Agency (EMA) at their reasoned request. According to national regulations, investigators or responsible people of the inspected sites might receive the inspection reports. All inspections are recorded on a European database operated by the Commission that is only accessible to them, the EMA and the competent authorities of the Member States. The results of the inspections shall be recognised by all the other Member States.

Inspections may be requested and coordinated by the EMA, within the scope of its power as provided for in Regulation (EEC) n°2309/93, especially in connection with clinical trials relating to applications through the centralised procedure.

The system requires a high level of confidence between Member States with respect to the national arrangements in place for managing, conducting and reporting GCP inspections, in order to deliver inspection results of a quality upon which the whole European Community can rely.

1. Introduction

Purpose and aims of this document.

The purpose of this document is to provide information on the structure, arrangements and procedures to be adopted by Member States, the EMA and the Commission in order to establish programs for the verification of compliance with GCP. Elements presented in this document should be considered as the basic minimum requirements for mutual acceptance of GCP inspections within the European Union. It is recognised that Member States will adopt the principles and guidelines of GCP, and establish compliance monitoring procedures in accordance with the Directive 2001/20/EC, their national legal and administrative practices.

Mission statement

By performing clinical trial inspections and providing clarifications on GCP requirements, inspectorates in the EU strive to enhance the level of compliance with regulations and good practices in the conduct of clinical trials, thereby enhancing the protection of the rights and welfare of study subjects and the quality of the data generated by these trials.

Inspections consist of the verification of compliance with GCP and applicable regulations and can take place during or after the conduct of clinical trials, and/or as part of the verification of applications for marketing authorisations (or follow-up to these). These inspections should be conducted according to procedures established in accordance with EU requirements in order to achieve acceptable standards to support mutual recognition of inspection findings. Improvement and harmonisation of inspection standards should be achieved by Member States, in collaboration with the Commission and the EMA, through joint inspections, agreed processes and guidance, and sharing of experience and training.

2. Scope

This document specifies the minimum requirements for a GCP inspection system to meet the requirements of Directive 2001/20/EC and assess the compliance with the requirements according to GCP of the parties involved in the trials with their obligations. This document does not cover GMP inspections related to clinical trials.

3. Definitions

When no specific definition is provided, the definitions established in Directive 2001/20/EC and the principles and detailed guidelines of good clinical practice are applicable.

National GCP compliance program: specific arrangement made by a Member State for verifying GCP compliance of the sites concerned by any clinical trial conducted and within the scope of this authority, inspections and trial data/document verification.

EMEA GCP compliance program: specific arrangement made by the EMEA, within the scope of its authority under Regulation (EEC) No. 2303/93, and the Member States, for verifying GCP compliance of the sites concerned by any clinical trial conducted that is subject to review by the CPMP, and within the scope of this authority, inspections and trial data/document verification.

Deviation from GCP or Non-compliance with GCP: failure to satisfy the prescribed requirements (ISO 10011-1).

Observation / finding: a failure to comply with the prescribed requirements recorded during the inspection and supported by appropriate factual evidence

4. Components of the system

4.1. Legal Basis

According to Directive 2001/20/EC, Member States shall appoint inspectors to inspect the sites concerned with 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 in order to verify compliance with the provisions of good clinical and manufacturing practice. The inspections shall be conducted by the competent authority of the Member State concerned, which shall inform the EMEA of these inspections; they shall be carried out on behalf of the Community and the results shall be recognised by all the other Member States. The EMEA shall coordinate inspections within the framework of its powers as provided for in Regulation (EEC) N°2309/93. Member states may request the assistance of other Member States. The Commission on the reasoned request of a Member State, or on its own initiative or a Member State may propose that an inspection be conducted in a third country, by Community inspectors (subject to any arrangements which may have been made between the Community and Third countries).

Directive 2001/83/EC sets out in Annex 1 that all phases of clinical investigation, including bioavailability and bioequivalence studies, shall be designed, implemented and reported in accordance with good clinical practice. This Annex specifies requirements for the acceptance of clinical trials as part of marketing authorisation applications made in the EU, or follow-up to these. These requirements apply to clinical trials, and the sites conducting them, wherever they are located.

Regulation (EEC) N°2309/93 states that in order to promote the protection of human health and of consumers of medicinal products throughout the Community, and in order to promote the completion of the internal market through the adoption of uniform regulatory decisions based on scientific criteria concerning the placing on the market and use of medicinal products, the objectives of the EMEA shall be to provide the Member States and the institutions of the Community with the best possible scientific advice on any question relating to the evaluation of the quality, the safety, and the efficacy of medicinal products for human use, which is referred to it in accordance with the provisions of Community legislation relating to medicinal products. To this end, the EMEA shall undertake, within its Committees, the coordination of the verification of compliance with the principles of good clinical practice.

4.2. Administrative Structure, programs and documentation

According to provisions of Directive 2001/20/EC and Regulation (EEC) n° 2309/93 the Member States, the Commission, and the EMEA have different roles further elaborated below.

Member states should:

- publish documents relating to the adoption of GCP principles within their territories. Establish the legal or administrative framework within which their GCP inspection program operates, with definition of the powers of inspectors for entry into clinical trial sites and their access to data.
- define the scope and extent of the GCP inspection program, including the nature of clinical trials, products, activities and organizations covered. As a minimum this should include clinical trials falling within the scope of Directive 2001/20/EC.
- ensure that the competent authority is directly responsible for a 'team' of inspectors with characteristics presented in section 4.4. or is ultimately responsible for such a 'team'. The competent authority should have ultimate responsibility for determining the compliance with GCP and for taking action based on the results of the inspection which may be necessary.
- establish a set of procedures for verification of GCP compliance. This set should include the procedures which will be used to examine both the organizational processes and the conditions under which clinical trials are planned, performed, monitored and recorded. Where an inspection is performed at the request of CPMP and is co-ordinated by EMEA, national procedures should be consistent with and cover the procedures agreed by the ad hoc meetings of GCP inspection services. A basic set of such procedures is available in Appendix I to this document.
- publish documents providing criteria which form the basis for the GCP compliance program, including information on the legal or administrative framework within which the program operates and references to published acts, normative documents (e.g. regulations, codes of practice).
- maintain records of national and international inspections (and the GCP compliance status if applicable) and of their follow-up.
- establish a process for requesting inspections/assistance from other Member States, in line with Directive 2001/20/EC article 15.1. and may cooperate in performing inspections at sites in one or other Member State and/or in third countries.
- establish a process for arranging inspections in third countries.
- enter in the Eudract database a reference to the inspections carried out on conformity with GCP according to provisions of article 11 of directive 2001/20/EC.

To foster international understanding and liaison, Member States should inform the Commission, the EMEA and other Member States of the nature and availability of the documentation on GCP which has been produced, together with the addressee(s) and telephone number(s) of the contact point(s) for GCP inspections.

Commission and EMEA should:

- establish a GCP inspection program for clinical trials falling within the remit of Regulation (EEC) 2303/93. The scope and extent of the program, the powers under which it is conducted, and the categories of inspections should be defined.
- establish, in conjunction with the Ad Hoc Meeting of GCP Inspection Services, the processes for the request, conduct, reporting and follow-up of the GCP inspections involved in this program. This is carried out through the inspectorates of the competent authorities of the Member States (and of those states participating in the Centralised Procedure).

- establish the process for contracting the conduct of inspections by the inspectorates of the Member States in accordance with the agreements established between the EMEA and the Competent Authorities of the Member States, (and of those states participating in the Centralised Procedure).
- publish documents providing criteria which form the basis for the GCP compliance program, including information on the legal or administrative framework within which the program operates and references to published acts, normative documents (e.g. regulations, codes of practice).
- maintain records of the inspections requested, the reports and their follow-up.
- establish a process for arranging inspections in third countries.

At the request of the EMEA, within the framework of its powers as provided for in Regulation (EEC) No 2309/93, or of one of the Member States concerned, and following consultation with the Member States concerned, the Commission may request a new inspection should verification of compliance with the Directive 2001/20/EC reveal differences between Member States.

4.3. Confidentiality

As competent authorities may have access to personal medical data and commercially valuable information and, on occasion, may even need to remove/take copies of sensitive documents from a clinical trial site or refer to them in detail in their reports,

Member States should:

- make provision for the maintenance of confidentiality, not only by inspectors but also by any other persons who are given access to confidential information as a result of GCP compliance monitoring activities;
- ensure that inspection reports are made available only to the recipients referred to in article 15.2. of directive 2001/20/EC, in accordance with their national regulations and subject to any arrangements concluded between the community and third countries. National regulations can make provisions for other recipients to receive the inspection reports.

Likewise the Commission and the EMEA should:

- make provision for the maintenance of confidentiality, not only by their personnel and by experts including inspectors, but also by any other persons who are given access to confidential information as a result of GCP compliance monitoring activities;
- ensure that inspection reports are made available only to the recipients referred to in article 15.2. of directive 2001/20/EC, in accordance with their regulations and subject to any arrangements concluded between the community and third countries. The EMEA and the Ad Hoc Meeting of GCP Inspection Services can make provisions for other recipients, for example the people responsible for the site/activities inspected, or the applicant for a Marketing Authorization/Marketing Authorization Holder.

Likewise the Ethics Committees and other recipients should:

- make provision for the maintenance of confidentiality, not only by their personnel and by experts, but also by any other persons who are given access to confidential information as a result of GCP compliance monitoring activities of which they are informed.

4.4. Personnel and training

As qualifications of inspectors are detailed in specific guidelines referred to in article 15.5. of Directive 2001/20/EC, only main points concerning this topic are repeated in the competent authority section.

Each competent authority should:

- ensure that an adequate number of inspectors is available.

- ensure there is sufficient resource to ensure availability of competent inspectors to work according to contracts between EMEA and the competent authority in the case of inspections requested by the CPMP.
- ensure that inspectors are adequately qualified and trained for their assigned duties.
- ensure the inspectors sign a Declaration of interests to make public the existence of any financial or other ties to inspected parties. Where needed this should be taken into consideration when nominating inspectors for a specific inspection.
- provide inspectors with a suitable means of identification (e.g., an identity card).

The Commission and the EMEA should ensure that:

- an adequate number of staff is available to support the requirements of the EMEA inspection program;
- an adequate number of staff is available to support the activities of the Ad Hoc Meeting of GCP Inspection Services;
- these staff are adequately qualified and trained for their activities;
- these staff meet the requirements of the Commission and EMEA concerning declaration of conflicts of interest;
- establish a list of experts from the Competent Authorities of the Member States, who are appointed by the latter to conduct inspections on behalf of the EMEA.

4.5. Follow-up to inspections

When an inspection has been completed, the inspector should prepare an inspection report. This report must be available to the sponsor while safeguarding confidential aspects. It may be available to the other Member States, to the Ethics committee and to the EMEA, in accordance with article 15.2. of directive 2001/20/EC, in accordance with the national Member State regulations, with those governing the Commission and the EMEA and subject to any arrangements concluded between the community and third countries.

Competent authorities of Member States should take action where deviations from GCP principles are found during or after an inspection. The appropriate actions should be described in documents from the competent authority.

Where a competent authority has objective grounds for considering that the sponsor or the investigator or any other person involved in the conduct of the trial no longer meets the obligations laid down, it shall forthwith inform him thereof, indicating the course of action which he must take to remedy this state of affairs. The competent authority concerned shall forthwith inform the Ethics Committee, the other competent authorities, EMEA and the Commission of this course of action.

Where a Member State has objective grounds for considering that the conditions in the request for authorization referred to in Article 9(2) of Directive 2001/20/EC are no longer met or has information raising doubts about the safety or scientific validity of the clinical trial, it may suspend or prohibit the clinical trial and shall notify the sponsor thereof. Such decision might be based on or caused by inspection findings. Before the Member State reaches its decision it shall, except where there is imminent risk, ask the sponsor and/or the investigator for their opinion, to be delivered within one week. In this case, the competent authority concerned shall forthwith inform the other competent authorities, the Ethics Committee concerned, the EMEA and the Commission of its decision to suspend or prohibit the trial and the reasons for the decision.

Competent authorities may also take action through the courts, where warranted by circumstances and where national legal provisions so permit.

Where applicable, if serious deviations are found which may affect the authorization of a clinical trial site, the competent authority should inform the authority responsible for the site authorization.

Where serious deviations are found which may have affected specific studies, the national competent authority should consider the need to inform the competent authorities in other Member States, the EMEA and the Commission of their findings.

Where an inspection is conducted as part of the EMEA inspection programme the EMEA and Commission should take action where deviations from GCP principles are found during or after an inspection. The appropriate actions should be described in documents agreed by the EMEA and the Commission within the powers conferred by Community legislation. This action may be taken directly against the Applicant or Marketing Authorization Holder or other involved party, or the EMEA or Commission may request the Member State concerned to take action. Independently, administrative or legal actions may be taken by the competent authorities on their territories in accordance with national regulations.

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Appendix 1: PROCEDURES

The list presented in the following table, referred to in section 4.2. of the guideline, represents the basic set of procedures for verification of compliance. This list represents the core set of procedures and these may be supplemented as required to address the needs of the inspection programs, advances in practice of inspection or advances in the conduct of clinical trials and investigational medicinal products. These procedures are adopted by the national Competent Authorities regarding national inspection programmes and those involving marketing authorisations via the mutual recognition process and by the Ad Hoc Meeting of GCP Inspection Services regarding EMEA Coordinated Inspections.

Minimum subjects to be covered by the procedures	National inspection	EMEA coordinated inspections
Preparation, adoption and maintenance of inspection program	X	X
Selection of the relevant trials/sites to be inspected according to the GCP compliance programme	X	X
Coordination of GCP inspections during assessment of applications submitted to the EMEA		X
Coordination / co-operation with other organisations involved in assessing GCP requirements <ul style="list-style-type: none"> - context of assessment of applications for national M.A. - inspection requests from other EU regulatory authorities - other 	X X X	
Preparation of inspections <ul style="list-style-type: none"> - assessment of applications submitted for a M.A. - surveillance of clinical trials / national program - authorisation/certification of a site (where applicable according to local regulation) 	X X (X)	X
Conduct of inspections <ul style="list-style-type: none"> - Common aspects - GCP inspection at the investigator site - GCP inspection at the laboratory/technical/technical site - GCP inspection at the sponsor/CRO site 	X X X X	X X X X
Preparation of inspection reports <ul style="list-style-type: none"> - context of assessment of applications for M.A. - surveillance of clinical trials / national program - authorisation/certification of a site (where applicable according to local regulation) 	X X (X)	X
Record keeping and archiving of documents obtained or resulting from the inspection	X	X
Actions taken after completion of inspection	X	X
Communication <ul style="list-style-type: none"> - handling and distribution of inspection reports - exchange of information; freedom of information 	X X	X X