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<b>RECOMMENDATION ON INSPECTION PROCEDURES FOR THE VERIFICATION OF GOOD CLINICAL PRACTICE COMPLIANCE July 2006</b>
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## **1. INTRODUCTION**

Good Clinical Practice inspections are performed in order to verify protection of the rights and welfare of trial subjects, compliance with the provisions of Good Clinical Practice and the quality of data generated in clinical trials.

This document should be read in conjunction with Article 15(5) of Directive 2001/20/EC and Chapter 6 of Directive 2005/28/EC.

## **2. SCOPE**

This document specifies and provides guidance on the minimum requirements for Good Clinical Practice inspection procedures to verify compliance with Good Clinical Practice in accordance with the requirements of Directive 2001/20/EC and Directive 2005/28/EC.

## **3. DEFINITIONS**

Deviation from Good Clinical Practice or non-compliance with Good Clinical Practice: failure to satisfy the prescribed requirements.

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

Good Clinical Practice Inspection Services Group: This group provides expert advice and support to the Community, its members, the European Commission, the European Medicines Agency and its scientific committees and other parties as required on matters related to Good Clinical Practice and inspections. It draws its membership from representatives of the Good Clinical Practice inspectorates of the Member States and the European Medicines Agency Inspection Sector.

## **4. COMPONENTS**

### **4.1. Administrative structure and documentation**

According to provisions of Directive 2001/20/EC, Directive 2005/28/EC and Regulation (EC) No. 726/2004 the Member States, the Commission, and the Agency have different roles further elaborated below.

Member States should:

- establish the legal and administrative framework within which their good clinical practice inspections operate, including provisions that inspectors of the competent authority of the other Member States also have access to the clinical trial sites and data, on request and where appropriate.
- provide for sufficient resources and should in particular appoint an adequate number of inspectors to ensure effective verification of compliance with good clinical practice.
- establish relevant procedures that should include
  - the modalities for examining both the study management procedures and the conditions under which clinical trials are planned, performed, monitored and recorded, as well as follow-up measures;

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- appointment of experts for accompanying inspectors in case of need;
  - requesting inspections/assistance from other Member States, in line with Article 15(1) of Directive 2001/20/EC and for cooperating in inspections in another Member State;
  - arranging inspections in third countries.
- maintain records of national and, if applicable, international inspections including the good clinical practice compliance status, and of their follow-up

According to Article 29 of Directive 2005/28/EC in order to harmonise the conduct of inspections by the competent authorities of the different Member States, guidance documents containing the common provisions on the conduct of those inspections shall be published by the Commission after consultation with the Member States.

These guidance documents should normally be developed by the Good Clinical Practice Inspection Services Group on the request of the Commission. Appendix I provide the topics covered by these guidance documents.

Member States enter in the EudraCT database a reference to the inspections carried out on conformity with Good Clinical Practice according to provisions of Article 11 and Article 15.1 of Directive 2001/20/EC and the guidance referred to in these articles.

To foster international understanding and liaison, Member States should inform the Commission, the Agency and other Member States of the national requirements relating to the adoption of Good Clinical Practice, the legal administrative framework for Good Clinical Practice inspections and the contact point(s) for Good Clinical Practice inspections.

The Agency in conjunction with the Good Clinical Practice Inspection Services Group should within the remit of Regulation (EC) No. 726/2004:

- establish the inspection procedures for inspections requested by the Agency;
- establish a Good Clinical Practice inspection program for clinical trials. The scope and extent of the program, the powers under which it is conducted, and the categories of inspections should be described;
- establish, in conjunction with the Good Clinical Practice Inspection Services Group, the processes for the request, conduct, reporting and follow-up of the GCP inspections. This is carried out through the inspectorates of the Member States;
- establish the process for contracting the conduct of inspections to the inspectorates of the Members States in accordance with the agreements established between the Agency and the Competent Authorities of the Member States;
- publish documents providing criteria which form the basis for the Good Clinical Practice 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) after validation by the Good Clinical Practice Inspection Services Group;
- maintain records of the inspections requested, the reports and their follow-up;

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- establish a process for arranging inspections in third countries.

At the request of the Agency, within the framework of its powers as provided for in Regulation (EC) No. 726/2004 , 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.

## **4.2. Confidentiality**

According to Article 21(1) of Directive 2005/28/EC inspectors, appointed by the Member States pursuant to Article 15(1) of Directive 2001/20/EC, shall be made aware of and maintain confidentiality whenever they gain access to confidential information as a result of good clinical practice inspections in accordance with applicable Community requirements, national laws or international agreements.

Inspectors of the Member States 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 shall according to Article 30 of Directive 2005/28/EC lay down all necessary rules to ensure that confidentiality is respected by inspectors and other experts. With regard to personal data, the requirements of Directive 95/46/EC of the European Parliament and of the Council (1) shall be respected.

Inspection reports shall be made available by the Member States to the recipients referred to in Article 15(2) of Directive 2001/20/EC, in accordance with national regulations of the Member States 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, for example the (principal) investigator or the people responsible for the site/activities inspected, or the applicant for a Marketing Authorization/Marketing Authorization Holder.

For inspections carried out in to the context of Article 23(2) of Directive 2005/28/EC the Agency should make provision for the maintenance of confidentiality, by their personnel involved and by the inspectors and by experts including inspectors who undertake the tasks of inspection and assessment on behalf of the Agency and its scientific committees. And ensure that inspection reports are made available to the recipients referred to in article 15(2) of Directive 2001/20/EC, in accordance with EU regulations and national regulations of the Member States and subject to any arrangements concluded between the community and third countries.

## **4.3. Follow-up to inspections**

When an inspection has been completed, the inspector should prepare an inspection report, provided to recipients presented in section 4.2.

According to Article 12 of Directive 2001/20/EC where a competent authority has objective grounds for considering that the sponsor or the investigator or any other person/party involved in the conduct of the trial no longer meets the obligations laid down, it shall forthwith inform

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him in writing 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 in writing, the other competent authorities, 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 Agency and the Commission of its decision to suspend or prohibit the trial and the reasons for the decision.

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

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

Where an inspection is conducted as part of the inspection programme for the centralised procedure, the Agency and Commission should take action where major or critical deviations from Good Clinical Practice principles are found during or after an inspection, with recommendation to Member States which may take administrative or legal actions on their territories in accordance with national regulations. Member States are recommended to take administrative action in a harmonised manner.

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## APPENDIX 1: TOPICS TO BE COVERED BY PROCEDURES

This Appendix provides the topics to be covered by the guidance documents, referred to in section 5.1. This set of guidance documents will be developed by the Good Clinical Practice Inspection Services Group and will be published by the Commission. These guidance documents may be customised or updated as required to address the needs of the scope of inspections, advances in inspection practices or advances in the conduct of clinical trials and/or advances in investigational medicinal products.

Procedures for national inspections are adopted by the Member States; in order to achieve harmonization amongst the EU inspectorates, Member States should ensure that the national procedures concerning topics covered by the guidance documents developed and adopted by the Good Clinical Practice Inspection Services Group, are consistent with those guidance documents and encompass the topics included. These national procedures are also applicable to marketing authorisations via the mutual recognition process.

Procedures involving marketing authorisations via the centralised procedure are adopted by the Good Clinical Practice Inspection Services Group, and are consistent with the guidance documents referred to in section 5.1 and encompass the topics included.

**Table I:** Topics to be covered by the generic set of procedures

Selection of the trials/sites to be inspected
- context of assessment of applications for marketing authorisation
- surveillance of clinical trials in Member States
Coordination / co-operation with other organisations involved in assessing Good Clinical Practice requirements
Preparation of Good Clinical Practice inspections
Conduct of Good Clinical Practice inspections
Preparation of Good Clinical Practice inspection reports
Record keeping and archiving of documents obtained or resulting from the Good Clinical Practice inspection
Actions taken after completion of Good Clinical Practice inspection
Communication on Good Clinical Practice inspections and findings