EUROPEAN COMMISSION
ENTERPRISE and INDUSTRY DIRECTORATE-GENERAL

Consumer goods
**Pharmaceuticals**

# GUIDANCE DOCUMENTS CONTAINING THE COMMON PROVISIONS ON THE CONDUCT OF GCP INSPECTIONS BY COMPETENT AUTHORITIES OF THE DIFFERENT MEMBER STATES

# Annex IV
# TO GUIDANCE FOR THE CONDUCT OF GOOD CLINICAL PRACTICE INSPECTIONS
# Sponsor and CRO

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*This document forms part of the guidance documents containing the common provisions on the conduct of GCP inspections . Please check for updates in the Volume 10 of the Rules Governing Medicinal Products in the European Union.*
*http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm*

# 1 INTRODUCTION

This annex compiles specific items that may be verified at the sponsor site or the CROs performing sponsor's trial-related duties.

There could be two different approaches:
- *System inspection (developed under Section 2)*
- *Specific clinical trial inspection (developed under Section 3)*

The selection of the items, which will be inspected, will depend on the scope of the inspection and should be established in the local inspection plan. In general, an appropriate sample of data/documents/items from specific trials should be checked during the inspection, to confirm the functioning of the process described. Where specific trials form part of the inspection request, this sample will come primarily from these trials.

# 2 SPONSOR OR CRO QUALITY SYSTEM INSPECTION

The aim of this kind of inspection is to evaluate the quality assurance and quality control systems established by the sponsor/CRO in order to assure that clinical trials are conducted and data are generated, recorded and reported in compliance with the protocol, GCP and applicable regulatory requirements.

The following items should be reviewed in a sponsor/CRO system inspection:

## 2.1 Organisation and personnel

The aim is to evaluate if the sponsor/CRO has a well-established organisation for clinical research activities and has a sufficient number of properly qualified and trained personnel for each area.

Review:
- Organisational charts that identify the key personnel in each area.
- The independence of the quality assurance unit.
- The job description, qualifications and training of the individuals involved at any stage of the clinical trial process.

## 2.2 Facilities and equipment

The aim is to identify and evaluate the facilities (e.g. archiving, investigational medicinal product storage) as well as the equipment used. Special attention should be paid to computer systems (hardware, software, communication, etc.), in order to evaluate their validation status, and their adequacy for the requirements of the trial(s) being inspected.

## 2.3 Sponsor/CRO Operating Procedures

Procedures should be reviewed in order to verify their compliance with GCP standards and applicable regulations.

### *2.3.1 Implementation and termination of the clinical trial*

The aim is to evaluate the procedures established for the implementation and termination of the clinical trial.

Review the procedures for:
- Document preparation: format and content and distribution of protocol, protocol amendments, informed consent documents, investigator brochure, CRF and any other trial documents.
  - Investigators selection and training.
  - Regulatory compliance: obtaining IEC approval/favourable opinion and necessary authorisations as required by EU requirements as set out in Eudralex Volume 10 and local regulatory requirements.

### *2.3.2 Monitoring*

The aim is to evaluate the system established for monitoring clinical trials.

Determine if procedures include:

- Description of monitoring activities: planning, frequency, extent and nature of monitoring activities (visits, data review, etc.).
- Content, handling and follow up of monitoring reports.
- Agreements for direct access to source documents by the sponsor personnel (or their appointed representatives) and by regulatory authorities and confidentiality of information about subjects.

### *2.3.3 Investigational Medicinal Product*

The aim is to determine if sponsor's procedures for different stages of the investigational medicinal product cycle are in accordance with current EU GMP and GCP requirements.

Determine if these procedures establish provisions for:

- Quality control requirements.
- Manufacturing, packaging and labelling.
- Storage and transport.
- Supplying, accountability, returns and destruction.
- Randomisation and code breaking.

### *2.3.4 Sample management*

The procedures established for handling samples obtained in clinical trials should be reviewed.

### *2.3.5 Safety and adverse events reporting*

The aim is to verify procedures for reviewing and communicating findings that could adversely affect the safety of subjects and the reporting of serious adverse events to regulatory authorities, investigators and IECs, where applicable.

Review procedures for:

- Identification of AE/SAE/SUSAR by the investigator and/or sponsor.
- Expedited Adverse Drug Reaction reporting to regulatory authority(ies), investigators and IEC, where applicable.
- Serious adverse events notification by investigators.
- Management of the serious adverse events reported by investigators.
- Safety updates and periodic safety reports.
- Validation of computer systems used.

### *2.3.6 Data handling and clinical trial report*

The aim is to evaluate the system established by the sponsor/CRO for handling the data obtained during the clinical trial and reporting it in the clinical trial report.

Determine if the procedures establish:

- Data handling, data analysis and their control procedures.
- Clinical trial report preparation according to ICH standards.
- Validation of the computerised systems used.
- Audit trails (for paper and computer systems).

### *2.3.7 Documentation archiving*

The aim is to determine whether the system established by the sponsor/CRO guarantees that the general documentation which has to be archived at the sponsor/CRO site (according to Eudralex Volume 10, chapter V, Recommendations on the content of the trial master file and archiving) is available, complete and maintained in good conditions during the period of time established.

Determine if procedures include:
- System for archiving and retrieval of documents.
- Controlled access to the archives.

### *2.3.8 Sponsor audit and quality assurance system*

The aim is to determine if the sponsor/CRO has established an audit system, as part of its own quality assurance system, in order to evaluate its activities related to clinical trials.

It should be determined if the procedures include:
- Audits of key clinical trial processes, including monitoring, data management, safety reporting, clinical study report production, archiving and computer system validation activities.
- Audits of contractors/sub-contractors.

The inspectors should also review:
- The processes for communicating and addressing audit findings, including the format and distribution of audit reports.
- The procedures for dealing with serious and/or persistent GCP non-compliance.
- Audit trails.
- Procedures for generation and implementation of audit programme(s)/plan(s).

### *2.3.9 Delegation of duties*

The aim is to verify the procedures for contracting/subcontracting of trial-related duties.
Inspectors should examine the procedures related with:
- Pre-selection and ongoing assessment of contractor/subcontractors.
- Documentation of duty delegation and its time recording.
- Handling contract amendments.
- Contracts should be reviewed (either specific ones or a sample).

## 3 SPECIFIC CLINICAL TRIAL INSPECTION

The aim of this type of inspections is to verify if the trial has been conducted, data has been generated, documented and reported in compliance with the protocol, GCP principles and sponsor procedures. The procedures and requirements applicable at the time of the trial should be considered and compared where relevant to those applicable at the time of the inspection.

The specific clinical trial inspections could also be conducted to answer questions listed in the request for a GCP inspection.

The aspects that should be checked are:

### 3.1 Implementation and termination of the clinical trial

The aim is to determine if all legal and administrative aspects of the clinical trial have been accomplished.

Review:
- Distribution of sponsor's duties or functions.
- Information given to investigators and/or specific training.
- Investigator selection and agreements.
- Fulfilment of regulatory requirements: IEC approval/favourable opinion and necessary authorisations.
- Submission and approval of amendments.
- Critical dates: IEC approval/favourable opinion, regulatory authorisation (where required) initiation of the study, patient enrolment period, closing of the trial sites, termination of the study.

### 3.2 Monitoring

Check:

- Monitoring plan/SOPs (availability, content and compliance with it).
- Frequency and extent of the monitoring activities made.
- Monitors' qualifications.
- Monitoring visit reports and the review of the reports by sponsor/CRO.
- Corrective actions induced by monitoring visits.

### 3.3 Investigational Medicinal Product

Check:

- Manufacturing, packaging, labelling and quality control.
- Supplying, accountability, returns and destruction (investigational medicinal product tracking system).
- Randomisation and code breaking.
- Blinding.
- Shipment.
- Condition of shipped product on receipt and during storage.

### 3.4 Safety and adverse events reporting

Check:

- Notification, follow up and reporting of serious adverse events and other non-serious adverse events requiring expedited reporting according to the protocol.
- Safety updates and their communication.

### 3.5 Case Report Form data verification

A selected number of CRFs should be checked to verify:

- Adherence with the protocol as well as data accuracy, completeness, legibility and timeliness.
- CRF corrections.
- Correspondence of the dates of first patient included and last patient with the dates of the study initiation and completion as well with investigational product delivery.

### 3.6 Data handling and clinical trial report (CTR)

Check:

- Data tracking system from CRF to the database.
- Validation of computer systems used.
- Data Management.
- Statistical analysis as established in the protocol.
- Clinical trial report content.
- Quality control applied.
- System for review of CTR, including signatures.

### 3.7 Clinical trial documentation and archiving

Determine if all essential documents listed in the Eudralex Volume 10, chapter V, Recommendations on the content of the trial master file and archiving, are available during the inspection.

### 3.8 Audit

Determine:

- If the clinical trial was audited and if the audit reports exist.
- Qualifications of the auditors.

## 4 REFERENCES


- Directive 2001/20/EC 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.
- Directive 2005/28/EC 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 product.
- Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the community code relating to medicinal products for human use, as amended.
- Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.
- EUDRALEX Volume 10 - Clinical trials, of the Rules Governing Medicinal Products in the European Union.: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm