



European Medicines Agency  
Inspections

London, 20 September 2007  
EMEA/INS/GCP/197228/2005

Procedure no.: INS/GCP/2

## PROCEDURE FOR PREPARING GCP INSPECTIONS REQUESTED BY THE EMEA

### GCP Inspectors Working Group

**Applies to:** EMEA, EU/EEA Inspectorates

**Summary of scope:** This procedure describes the preparation for a GCP inspection requested by the EMEA.

**Keywords:** GCP Inspection, preparation

**Public**

**Supersedes:** N/A

**Finalisation**

**Date**

Adoption by the GCP Inspectors Working Group

05 September 2007

<b>1</b>	<b>INTRODUCTION</b>	<b>3</b>
<b>2</b>	<b>INSPECTION INITIATION</b>	<b>3</b>
<b>3</b>	<b>REVIEW OF DOCUMENTS AND INFORMATION</b>	<b>3</b>
<b>4</b>	<b>INSPECTION REQUEST VALIDATION</b>	<b>4</b>
<b>5</b>	<b>INSPECTION FILING AND ARCHIVING</b>	<b>4</b>
<b>6</b>	<b>INSPECTION PLAN</b>	<b>4</b>
<b>7</b>	<b>INSPECTION ANNOUNCEMENT</b>	<b>5</b>
<b>8</b>	<b>PRACTICAL PREPARATION</b>	<b>5</b>
<b>9</b>	<b>RESPONSIBILITIES</b>	<b>6</b>
9.1	RESPONSIBILITIES OF THE REPORTING INSPECTOR (RI)	6
9.2	RESPONSIBILITIES OF THE LEAD INSPECTOR (LI)	6
	<b>APPENDIX 1: DOCUMENTS/INFORMATION THAT MAY BE USED FOR REVIEW PRIOR TO THE START OF THE INSPECTION</b>	<b>7</b>
	<b>APPENDIX 2: ELEMENTS FOR AN INSPECTION PLAN</b>	<b>9</b>
1.	GENERAL ASPECTS	9
2.	GENERAL CONTENT	9
3.	LAYOUT OPTIONS	9
4.	SITUATIONAL ASPECTS	9
	<b>APPENDIX 3: MODEL LETTERS FOR ANNOUNCEMENT</b>	<b>10</b>
1.	TEMPLATE FOR THE ANNOUNCEMENT OF THE INSPECTION TO THE SPONSOR	10
2.	TEMPLATE FOR THE ANNOUNCEMENT OF THE INSPECTION TO INVESTIGATORS	11
	<b>APPENDIX 4: REFERENCES AND RELATED DOCUMENTS</b>	<b>13</b>

## **1 INTRODUCTION**

The scope of this document is to provide guidance for the preparation for GCP inspections requested by the EMEA. The responsibilities set out in the procedure for co-ordinating GCP inspections requested by the EMEA (INS/GCP/1) form the basis for this procedure. This guidance to preparing for the inspection may in principle be used in preparing for any type of inspection (see Procedure for conducting GCP inspections requested by the EMEA (INS/GCP/3), inclusive its annexes).

## **2 INSPECTION INITIATION**

The appointment of the Reporting Inspector and acceptance of that role is part of the procedure for co-ordinating GCP inspections requested by the EMEA (INS/GCP/1). Prior or during the process of the formal adoption of a GCP inspection request by CHMP, informal contacts and assessments (phone, fax, mail) and an evaluation of the inspection data base (when developed) will have helped define the context of the request. A decision on the scope of the inspection, the centres/sites and the composition of the inspection team based on need/availability/qualifications will also have been made. This will have resulted in the definitive inspection request.

At the moment the formal inspection request is issued, the Reporting Inspector (RI) has been appointed, contracts between the involved MS Inspectorates have been drawn up and contact points within the Inspectorates have been identified.

The RI formally receives a copy of the adopted CHMP/EMEA request according to the co-ordination procedure. This is the formal start of this procedure for the preparation for the inspection.

The MS Inspectorates involved will subsequently designate the Lead Inspectors (LIs) and the other members of the inspection team. The composition of each local team and any subsequent changes (see Section 4 of this procedure) are communicated to the RI and through him/her to the EMEA Inspection Sector. A contact point at the sponsor/applicant should be identified.

The RI contacts the contact point of the involved MS Inspectorates and the Lead Inspector(s) for the site inspections to confirm the start of the inspection and agree on and set the timelines.

The RI has to ensure that the LI(s) are provided with all documents they need and the RI has access to, for inspection preparation.

A request from the LI(s) for additional documents/information from the sponsor/applicant should be addressed through the RI. The RI is responsible for routing the requests for this documents/information, either through the EMEA Inspection Sector or directly to the sponsor/applicant, as agreed upon by RI and EMEA. According to the procedure for co-ordinating GCP inspections requested by the EMEA (INS/GCP/1), the preparation of the inspection should be completed within [20] days after the delivery of the documents requested from the sponsor/applicant.

## **3 REVIEW OF DOCUMENTS AND INFORMATION**

Essential information and documentation needs to be identified, obtained and reviewed. Necessary information needed to evaluate the essential aspect to be included in the conduct of the inspection, may be derived from a number of sources: the inspection request from CHMP, MA dossier, reference documents, guidelines, legislation, inspection SOPs (EU, local), international standards (ISO/CEN), local legal requirements (EU, third country), local field standards etc. A guide to the documentation that has to be available/gathered prior to the start of an inspection is listed in the appendix I to this procedure.

This obtained/collected information should be reviewed and evaluated by the RI and participating LI(s). The RI, in agreement with the LI(s), evaluates the CHMP request on the basis of the applicable/available documents and information. Results of this review will be incorporated into the inspection plan by the RI.

In case the sponsor/applicant fails to provide the RI with essential documents, or the submitted documentation is below the required standard, these objections will be notified to the sponsor/applicant in writing, with a deadline of seven calendar days for remedial action. If a response is not received within this timeframe, the RI should inform the EMEA and the LI(s) without delay.

The review of information of all aspects of the inspection could lead to the identification of additional technical and logistical needs (e.g. translation in case of language problems, transport feasibility).

Communication between the RI and the LI(s) will result in the definition of the site inspection team and formal assignment of the LI(s) and the language of the inspection at each site is agreed upon. In general this is the local language. The dates and places, of each inspection site are set by the LI(s) according to the local procedures. The LI(s) communicate this information to the RI, who checks that the formal timelines are not endangered.

#### **4 INSPECTION REQUEST VALIDATION**

The review of the documentation/information would routinely occur prior to the formal adoption of the request by the CHMP. As a result of this review the inspection team members may conclude that additional (external) expertise is necessary to complete (one or more of) the inspection teams at the various sites. This is relevant in respect to the qualification of the MS inspectors and the overall organisation of MS Inspectorates.

In case the need for external experts is declared, this has to be communicated from the LI(s) to the RI and through him/her to the CHMP/EMEA. This may also be a decision made entirely by the involved MS in case of additional expertise required for an inspection site inspected in that MS. This decision has to be announced to the RI. The RI will then incorporate this aspect into the inspection plan and extend the formal inspection team.

If the review of information and documentation results in a requirement for a modification of the original request, this must be communicated to the EMEA Inspection Sector by the RI. This change must be adopted by the CHMP prior to incorporation into the central and local inspection plans.

The RI will add the information on the formal acceptance and the composition of the complete inspection team and of the local inspection teams and add this information to the inspection files.

It is foreseen that review of the information/documentation available to the inspection team may, on occasion, lead to doubts/reflections about the scope of the inspection request. Reasons for this may be e.g. the irrelevance of a selected site, or the expectation that no relevant information will be resulting from the conduct of such an inspection. Also the feasibility of the timeliness should be taken into account. This will have to be communicated in writing to the CHMP, and the reasons substantiated, so that the CHMP is in the position to consider appropriate changes concerning the scope of the requested inspection and/or the selected sites.

#### **5 INSPECTION FILING AND ARCHIVING**

The RI should start the preparation of central inspection file for the inspection as soon as the inspection is initiated. The LI(s) participating in the inspection have to open Local Inspection Files. The format of these files should be in accordance with the format set out in Annex VI to the procedure for Conducting GCP Inspections requested by the EMEA ((INS/GCP/3/V).

#### **6 INSPECTION PLAN**

After the co-ordination of dates for the inspection, a central inspection plan is prepared by the RI and finalised in agreement with the LIs. Based on the central inspection plan, the LIs will prepare local inspection plans for each selected site. The detail of these inspection plans may vary. Routine inspection request may need less detail than for cause inspections, or inspections for specific products or systems.

The central inspection plan will be general in outline and define the relevant aspects of the clinical trial sites and scope that are to be covered during the inspection at the various selected sites. It will be based on the adopted CHMP request and the reviewed documentation.

The inspection plans (central and for each site) will incorporate the timelines for the practical organisation for the inspections at the sites, the timelines for the local report(s), as well as the dates whereby the IIR will have to be finalised according to the 'procedure for co-ordinating GCP inspections requested by the EMEA'(INS/GCP/1).

A checklist may be designed as part of the local inspection plan, in accordance with the local procedures.

Elements to be taken into account when drafting the inspection plan are listed in Appendix II.

## **7 INSPECTION ANNOUNCEMENT**

Once EMEA has announced the inspection to the applicant, the RI may announce the inspection to the inspectee/sponsor contact point.

The responsible personnel at the selected sites are informed of the forthcoming inspection according to the procedures of the MS Inspectorate. The applicant is informed of the inspection by the EMEA Inspection Sector according to the EMEA SOP: 'Procedure for co-ordinating GCP inspections requested by the EMEA'(INS/GCP/1). Standard models for announcement letters are found in appendix III.

Inspection dates for the selected sites are communicated to the sites, in accordance with the timelines in the site inspection plans.

The LI ensures that the relevant parts of the inspection plans are communicated to the responsible personnel at the site in according to the MS procedures. The RI is responsible for communication of relevant aspects to the contact point.

Occasionally the sponsor/MAH may ask for a pre-inspection meeting to discuss the scope of the inspection. The RI or LI(s) are under no obligation to agree to such a meeting. In case the RI or LI(s) feel that a pre-inspection meeting would be useful (particularly to clarify aspects of the scope for a complex inspection), the RI has the discretion to arrange such a meeting so long as it does not affect the overall timelines for the inspection and the sponsor/MAH undertakes to pay for the additional costs. The scope of the inspection as defined in the CHMP request must not be affected by the results this meeting.

## **8 PRACTICAL PREPARATION**

The need for preparation may differ between inspections, depending on the type of inspection, type of trial, therapeutic area and product, location of the inspection, number of selected sites, etc.

For third country inspections it may be convenient to have the applicant company help with the provision of air tickets, local transport and accommodation according to the itinerary set out by the inspection team.

For EU inspections, the LI may facilitate as much as possible, the practicalities for the other team members.

For third country inspection it may be essential to establish contact with the local inspectorates/authorities to inform them of the proposed inspection. Contact with foreign authorities (including EU candidates) should be established by the EMEA.

There may also be a need to ensure the availability for a translator in case the language used locally is not available within the inspection team. This service should be required from the sponsor.

## **9 RESPONSIBILITIES**

### **9.1 Responsibilities of the Reporting Inspector (RI)**

The RI is responsible for

- The communication with the CHMP/EMEA and the assessors of the Rapporteur/Co-rapporteur.
- The verification of the location of the sites and for the co-ordination of the inspection team.
- The preparation of the central inspection plan.
- Proposing and setting the timelines for the inspection activities (preparation, conduct, reporting).
- Starting the preparation of the inspection after formally receiving a copy of the CHMP/EMEA request according to the set procedures.
- Initiating the formal information flow to the MS lead inspectors (LIs).
- The sending of the submitted documentation and information to the LI(s) without delay.
- The review of the quality and completeness of the information together with the LI(s).
- Checking that the timelines are kept throughout the duration of all inspection facets. The timelines should be based on the CHMP request, where deadlines are set.
- Deciding (also at the request of the LIs) that more information is needed from CHMP/EMEA. The request is made by the RI on behalf of the inspection team to the EMEA Inspection Sector. The RI/LI may request additional documentation which deems to be necessary for the preparation of the inspection from the inspectee / sponsor
- The quality and security of the central inspection file.
- The timeliness and completeness of archiving the central inspection documentation and for ensuring that the inspection is conducted in accordance with the EU SOPs.
- Keeping the inspection documentation up to date and secure.
- Checking that the confidentiality requirements are adhered.

### **9.2 Responsibilities of the Lead Inspector (LI)**

The LI is responsible for:

- The conduct of the inspection at the site in accordance with the local SOPs, legal requirements and EU SOPs.
- The review of the information together with the RI.
- The preparation of the local inspection plan(s).
- Deciding that more information is needed from CHMP/EMEA. The request is made by the RI on behalf of the inspection team.
- The organisation and validation of the local team. The LI is team leader for the local inspection.
- The upkeep, quality and security of the local inspection files and for keeping the archives according to the local procedures.
- Ensuring that all local relevant reference documents are available and important local details/differences communicated to the RI.
- Adhering to the timelines.

## **APPENDIX 1: DOCUMENTS/INFORMATION THAT MAY BE USED FOR REVIEW PRIOR TO THE START OF THE INSPECTION**

### **1. EMEA/CHMP, Rapporteur/Co-Rapporteur**

adopted CHMP request  
EMEA Procedures  
Assessment Reports  
List of Questions, response to the LOQ

### **2. Overview of the conduct of the study:**

total number of sites/locations/countries  
inclusion rate, screening, randomisation, etc.  
SAEs, ADRs  
drop out frequency  
time frame of trial  
annual reports, final report  
presence of a similar/extension protocol

### **3. Sites**

investigator(s)/co-investigator(s) CVs and qualifications  
information on sites involved/selected (including e.g. pharmacy clinical departments  
X-ray, MRI, Echo, ECG, CT, CROs)

### **4. Lab**

local/central  
type of labs involved  
type of examinations/tests  
special equipment/procedures

### **5. Sponsor**

responsibilities defined in contracts  
CRO(s) involved  
protocol, amendments, investigator's brochure  
CRFs  
patient information and consent  
printout (of parts) of the clinical database  
quality management (QC, QA)  
sponsor SOPs related with the scope of the inspection

### **6. Trial Medication**

GMP  
manufacturing  
labelling  
blinding procedures  
randomisation list  
quality documentation

### **7. Ethics**

patient information/informed consent  
patient recruitment  
insurance  
up dates of safety information  
IEC opinion

### **8. Local inspectorate**

availability of qualified inspectors

availability of qualified GMP inspectors (if the scope of the inspection covers IMP)  
recruitment of external expertise  
time schedule

#### **9. Local legal regulations**

applicable GCP and legal requirements  
notification/approval of protocol  
importation of investigational products  
announcement of inspection to the competent authority  
insurance  
trial medication: import license, labelling, storage, destruction  
SAE reporting

#### **10. Data**

tabular listings of individual data

- per site
- per criteria

## **APPENDIX 2: ELEMENTS FOR AN INSPECTION PLAN**

### **1. General aspects**

- Items
- Support
- Timelines
- Expertise
- SOP
- Legalities

### **2. General Content**

- Agenda, Dates
- Sites, Facilities
- Team Members
- Systems
- Specifics

### **3. Layout options**

- Linear
- Modules
- Agenda with Addenda

### **4. Situational Aspects**

- Prospective
- Flexible

## APPENDIX 3: MODEL LETTERS FOR ANNOUNCEMENT

### 1. Template for the announcement of the inspection to the sponsor

<Headed paper, and name and address of inspector carrying out the inspection>

<Date>

<Local sponsor contact, name>

<Address>

**EMA Reference No. EMA/H/C<procedure number >, Centralised Application for <product name> GCP Inspection**

**Subject: GCP Inspection of <sites and protocol name/number>**

Dear <Local sponsor contact>,

The above mentioned clinical study has been included in the marketing authorisation application for <product name>.

In connection with the examination of the above application, the Committee for Medicinal Products for Human Use has asked for an inspection to be carried out of the conduct of the clinical study <protocol number>, in accordance with Article 57 of Council Regulation (EC) No. 726/2004.<include reference to national legislation as relevant>.

Your facility has been selected as part of this inspection process. The <national inspectorate name> is conducting this inspection on behalf of the European Medicines Agency. The lead inspector at your site will be <name> who will be accompanied by <names of other inspector/experts and their affiliation>. The inspection will be carried out at your facility at the following address: <sponsor site address>

We propose to conduct the inspection at your site on <dates>. We anticipate the inspection will last for <number> days. We will want to have an opening meeting of approximately 1½ hours at the beginning of the inspection with you and key members of your study team. There will also be a closing meeting of approximately 1½ hours with you and your team. During the inspection you and/or designated members of your team should be available, on occasions, to explain details of the study conduct or to assist in locating documents and data.

You will need to ensure that all relevant departments and personnel are notified. They should be ready for inspection and have relevant documentation (including the local Trial Master File, Standard Operating Procedures, Case Report Forms) and facilities available and accessible. We will require direct access to these records. We will also need to interview members of the clinical study team, in particular the monitors responsible for the sites during the study, and to visit facilities involved including <monitoring, data management, clinical safety – include as required>. We will also be inspecting the following clinical investigators/<other facilities as appropriate> monitored/managed by your site. We may require access to relevant databases and/or printouts from these during the inspection.

Please ensure that there is a room where we can work, reviewing records and interviewing members of the study team. There should be a desk/table and chairs and we will need access to a phone, fax and photocopier. There will be <number of inspectors> inspectors present.

Please confirm your availability on these dates and that the address for the inspection is the appropriate one for the activities to be inspected. If there are any difficulties with the availability of the relevant personnel, documents or facilities please notify us immediately.

If you need any further information about the procedure to be followed for the inspection please contact me at the above address. We look forward to meeting you and your team.

## **2. Template for the announcement of the inspection to investigators**

*<Headed paper, and name and address of inspector carrying out the inspection>*

*<Date>*

*<Principal Investigator, name>*

*<Address>*

**EMEA Reference No. EMEA/H/C< procedure number>,  
Centralised Application for <product name>  
GCP Inspection**

**Subject: GCP Inspection of < protocol name/number>**

Dear *<Principal Investigator name>*,

The above mentioned clinical study, including the work of your centre has been included in the marketing authorisation application for *<product name>*.

In connection with the examination of the above application, the Committee for Medicinal Products for Human Use has asked for an inspection to be carried out of the conduct of the clinical study *<protocol number>*, in accordance with Article 57 of Council Regulation (EC) No. 726/2004. *<include reference to national legislation as relevant>*.

Your site has been selected as part of this inspection process. The *<national inspectorate name>* is conducting this inspection on behalf of the European Medicines Agency (EMA). The lead inspector at your site will be *<name>* who will be accompanied by *<names of other inspectors and their affiliation>*. The inspection will be carried out at your site at the following address: *<site address>*

We propose to conduct the inspection at your site on *<dates>*. We anticipate the inspection will last for *<number>* days. We will want to have an opening meeting of approximately 1½ hours at the beginning of the inspection with you and key members of your study team. There will also be a closing meeting of approximately 1½ hours with you and your team. During the inspection you and/or designated members of your team should be available, on occasions, to explain details of the study conduct or to assist in locating documents and data.

You will need to ensure that all relevant departments and personnel are notified. They should be ready for inspection and have relevant documentation (including study related files, procedures, Case Report Forms, source documents and medical records) and facilities available and accessible. We will require direct access to these records. We will also need to interview members of the clinical study team and to visit facilities involved in this clinical study including the pharmacy, clinical laboratory *<include departments/personnel as relevant>*.

Please ensure that there is a room where we can work, reviewing records and interviewing members of the study team. There should be a desk/table and chairs and we will need access to a phone, fax and photocopier. There will be *<number of inspectors>* present.

Please confirm your availability on these dates and that the address is the address of the site where the study was conducted. If there are any difficulties with the availability, at this site, of the relevant personnel, documents or facilities please notify us immediately.

If you need any further information about the procedure to be followed for the inspection please contact me at the above address. We look forward to meeting you and your team.

Yours sincerely,

<Lead Inspector>

cc: <names> Inspection team members, <name> EMEA inspections sector, <name(s) Sponsor/Applicant contact>.

## **APPENDIX 4: REFERENCES AND RELATED DOCUMENTS**

See "Principal documents taken into account for the preparation of procedures for GCP inspections requested by the EMEA"