EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods
Pharmaceuticals

Brussels, 8 June 2009
ENTR/F/2/SF/dn D(2009) 19000

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

GUIDANCE FOR COORDINATION OF GCP INSPECTIONS AND CO-OPERATION BETWEEN GCP INSPECTORS, THE REFERENCE AND CONCERNED MEMBER STATES AND CMD(h)[1], IN THE CONTEXT OF THE EVALUATION OF THE GCP COMPLIANCE OF MARKETING AUTHORIZATION APPLICATIONS FOR MUTUAL RECOGNITION AND DECENTRALIZED PROCEDURES

Document history:	
Date of adoption of draft by CMD:	1 December 2008
Date of adoption of draft by GCP Inspectors working group:	3 December 2008
Date of publication by the Commission:	8 June 2009
Date of coming into effect:	8 December 2009
Supersedes:	N/A
Reasons for revision:	N/A

Keywords: GCP Inspections, Cooperation of inspectors with Member States and CMD(h)

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.

[1] Coordination Group for Mutual Recognition and Decentralized Procedure (human)

TABLE OF CONTENTS

ABBREVIATIONS

- CHMP, Committee for Medicinal Products for Human Use
- CMD(h), Coordination Group for Mutual Recognition and Decentralized Procedure (human)
- CMS, Concerned Member State
- DCP, Decentralised Procedure
- EMEA, European Medicines Agency
- EU/EEA, European Union/European Economic Area
- GCP**,** Good Clinical Practice
- GCP IWG, GCP Inspectors Working Group
- MAA, Marketing Authorization Application
- MRP, Mutual Recognition Procedure
- NCA: National Competent Authority
- LI, Lead Inspector
- RI, Reporting Inspectorate
- RMS, Reference Member State
- IR, Inspection Report
- IIR, Integrated Inspection Report

1. PURPOSE

The intention of this document is to set out guidance for the coordination of good clinical practice ("**GCP**") inspections and co-operation between GCP inspectors, the Reference and Concerned Member States ("**RMS**", "**CMS**") and CMD(h), in the context of the evaluation of GCP compliance of Marketing Authorization Applications ("**MAA**s") in the mutual recognition and decentralized procedure ("**MRP**", "**DCP**"). The guidance covers GCP inspections to be carried out by the competent authorities of Member States in the context of the MRP and DCP.

The legal basis for this guidance document is Article 29 of Directive 2005/28/EC which requires that 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.

Any clinical trials conducted within the EU/EEA as well as clinical trials conducted outside the EU/EEA which relate to medicinal products which are being authorised or have been authorised for placing on the EU/EEA market might be subject to a GCP inspection.

In the context of the MRP and DCP, inspections may take place on any of the following occasions:

- as part of the verification of applications for marketing authorisation;
- as a follow-up to the granting of an authorisation.

The objective of a GCP inspection is to verify whether the clinical trial was conducted in accordance with applicable regulatory requirements (i.e. implemented provisions of Directives 2001/20/EC, 2005/28/EC, 2001/83/EC and 2003/63/EC) and considering all relevant guidance with respect to commencing and conducting clinical trials (e.g. CPMP/ICH/135/95 Note for Guidance on GCP).

The guidance relating to the conduct of inspections is published in Chapter IV of Volume 10 of the Rules Governing Medicinal Products in the European Union.

2. SCOPE

This guidance document applies only to the coordination of GCP inspections carried out by EU/EEA inspectors in connection with the marketing authorization of medicinal products in the MRP and DCP. This guidance does not apply to GCP inspections requested by the EMEA in the context of centralised application procedures nor to routine national inspection programmes, e.g. planned inspections unrelated to an authorisation application. However, this guidance does apply to all GCP inspections conducted in relation to an MRP/DCP application, whether it involves inspection activity in more than one Member State or not, as information will be shared with concerned Member States.

3. RESPONSIBILITIES

3.1. Requesting Party

The following parties may request GCP inspections in this context and are referred to as the "Requesting Party":

- CMD-h,
- National Competent authority ("**NCA**") (RMS or CMS),
- Committee for Medicinal Products for Human Use (CHMP). When there is a referral in accordance with Directive 2001/83/EC this guidance should be followed when the requesting party is not the CHMP. In those cases where the inspection is specifically requested by the CHMP, the "Procedure for coordinating GCP inspections requested by the EMEA" (INS-GCP-1) should be followed.

3.2. Reporting Inspectorate

The Reporting Inspectorate ("**RI**") is the inspectorate from a Member State which has the overall responsibility for the coordination of the inspection procedure and for the reporting and communication of the integrated inspection result. The RI assigns the Reporting Inspector.

Where only one Member State is involved, the inspection may follow the national procedures in that MS for conducting and reporting the inspection. The roles set out under 3.2 and 3.3 are all undertaken by that national inspectorate.

3.3. Reporting Inspector

The responsibilities of the Reporting Inspector are set out in the guidance relating to the preparation of GCP inspections published in Chapter IV of Volume 10 of the Rules Governing Medicinal Products in the European Union.

The Reporting Inspector has the following general duties in the context of this guidance:

- making arrangements for the appointment of the inspection team,
- distribution of the Inspection Request Form (Appendix 1) and Inspectors Appointment Form (Appendix 2) to the involved Lead Inspectors ("**LI**"s), where applicable (this may not be applicable for inspections conducted in a single MS in accordance with national procedures),
- writing and signing the Integrated Inspection Report ("**IIR**"),
- main communication point between the inspection team and the involved parties i.e. sponsor, applicant, NCA, RMS, CMD(h), the GCP Inspectors Working Group ("**GCP IWG**"), and in case of a referral, CHMP, EMEA.

The Reporting Inspector may also be the Lead Inspector (see below) for one or more sites.

3.4. Lead Inspector ("LI")

The responsibilities of the LI are set out in the guidance relating to the preparation of GCP inspections in Chapter IV of Volume 10 of the Rules Governing Medicinal Products in the European Union. The LI has also the following general duties:

- reviewing and co-signing the IIR, if applicable;
- entering the details of the inspection in the EudraCT database and in line with the procedure for the standardization of entries in EudraCT;
- informing the 3rd country responsible agency when sites in 3rd countries are inspected.

3.5. Inspection Report ("IR")

The preparation and signature of the Inspection report is detailed in the guidance for the preparation of GCP inspections reports in Chapter IV of Volume 10 of the Rules Governing Medicinal Products in the European Union.

In the context of this guidance, the IR will be written in English, unless required by local regulations to be in local language. In the latter case the IR will be translated/modified to English under the responsibility of the LI and this could take place prior to signature or after signature whenever all inspectors signing the report speak the local language.

3.6. Integrated Inspection Report (IIR)

The IIR is the integrated report which is prepared for each GCP inspection request whenever the inspection involves more than one inspection site. The IIR is not necessary when the inspection is carried out at one or more sites in only one MS where the national procedures foresees a single inspection report summarising the findings from all the sites inspected. In this case, the report should fulfil the objectives of both, the IIR and the IR.

This report should be written in English, and summarises the critical and major findings of the inspection of all sites involved. The report contains an overall evaluation of the quality of the data submitted and of the compliance with the regulatory requirements and the principles of GCP based on the findings from all inspected sites. Any finding that is process related and not site specific will also be highlighted in the IIR. The IIR also contains a conclusion on whether the quality of the data inspected as a whole or in parts may be used for the evaluation by the assessors regarding acceptance/non-acceptance of the trial data. The IIR conclusions should recommend any follow-up to be requested from the applicant or a further inspection if considered necessary.

It is written and signed by the RI, and reviewed and signed by the LIs. The IRs are attached to the IIR as appendices. Signature may be obtained by fax, and the originals mailed to the Reporting Inspector.

4. DESCRIPTION OF THE PROCEDURE

4.1. GCP Inspection Request

GCP inspections are initiated for different reasons, for example:

- to verify that organisations, institutions and facilities involved in the conduct of clinical trials have quality assurance arrangements in place which ensure the conduct of clinical trials in compliance with applicable regulatory requirements and GCP;

- to ensure that human subjects were protected from undue hazard or risk during the course of clinical trials and that internationally recognized ethical standards were applied;

- to verify that clinical data and information contained in the marketing authorisation application are scientifically valid and accurate;

- to examine clinical trials further because of, e.g.:

  – their importance for an application for marketing authorisation;

  – the recruitment of subjects from vulnerable groups or other ethical concerns;

  – concerns about the investigational medicinal product(s);

  – concerns about the credibility and accuracy of the data e.g. when the recruitment pattern appears to be unusual, when the efficacy, biological or safety results are inconsistent with regard to results of other studies or when the results of one site are significantly different from the others or when serious and/or persistent GCP non-compliance was reported before for the site and/or organisation subject to inspection.

To cope with the different focuses it is necessary to use variable approaches and inspection types.

The request for a GCP inspection is made by the requesting party (see chapter 3.1).

The GCP Inspection Request Form (Appendix 1) should be completed by the requesting party. This should clearly address the grounds and scope of the inspection, the site(s) and, if applicable, a list of specific questions to be addressed during the inspection and anything else relevant to the inspection.

First contact point for the requesting party is the potential RI (see section 3.2). After the appointment of the RI, the timeline for the conduct of the inspection and the availability of the IR/IIR should be drafted by the requesting party in agreement with the RI. The scope of the inspection and the selection of the sites to be inspected should be discussed and agreed between the assessors and inspectors. Contacts between the requesting party and the RI should take place as early as possible during the evaluation process.

Additionally the inspectors should check whether any GXP inspection results are available or any GXP inspections are requested for the same application, trial, organisation(s), institution(s) or facility/ies.

The RI communicates the draft request, the draft timelines and other relevant issues with the relevant inspectorates and gives feedback to the requesting party.

4.2. Designation of the Reporting Inspectorate

Where an inspection is required for an MRP or DCP the inspectorate of the RMS should assume the task of the RI. However, if under exceptional circumstances (e.g. temporarily insufficient personnel resources), the RMS

inspectorate cannot fulfil this task, then the following sequence should be followed for the designation of the RI:

- The Member State where the inspection will take place;
- The inspectorate(s) of the CMS(s);
- Another Member State.

In this case the RMS inspectorate may participate as a co-inspectorate. The enquiries relating to designation of the RI should be made using the Inspection Enquiry Form (see Appendix 3).

For CHMP referrals, the inspectorate of the Rapporteur or Co-Rapporteur MS should assume the task of the RI whenever the requesting party is the CHMP in accordance with the "Procedure for coordinating GCP inspections requested by the EMEA" (INS-GCP-1). If the CHMP is not the requesting party, then the above criteria will apply.

4.3. Designation of the Inspection Team

An inspection team should preferably consist of at least two inspectors. There is one LI for any given inspection site (this may be the same or different inspectors for the different sites selected).

Where an inspection site is located in the EU/EEA the LI will be from the inspectorate in the country where the site(s) to be inspected is located. In case the LI and the RI are not from the same Member State, the inspection should preferably be performed as joint inspection. The Inspection Enquiry Form (see Appendix 3) together with the draft inspection request (see section 4.1) should be sent to the single point(s) of contact of the respective Member State(s).

For inspection in third countries the LI for each site is agreed by the inspection team.

In order to ensure the presence of skills necessary for specific inspections, the RI(s) or LI(s) may appoint additionally experts with appropriate qualifications and experience to fulfil collectively the requirements necessary for conducting the inspection.

Member States, which are involved in the application, may send trainees, subject to considerations of the size of the inspection team and agreement with the LI.

If the initial proposal for the inspection was made by the CMS, this inspectorate may also be involved in the inspection.

4.4. Communication of the Inspection Request to the Reporting and Lead Inspectorates and Appointment of Inspectors

The requesting party sends the final Inspection Request Form as soon as possible to the RI.

The RI countersigns the Inspection Request Form and forwards copies to the requesting party and in parallel, where applicable, to the participating LIs.

The RI and the LI(s) shall confirm their role by dating and signing the Inspectors Appointment Form (see Appendix 2).

At this point of time the inspection will be announced to the sponsor and applicant, in case they are not the same, by the RMS. Detailed information is given in the Guidance for the Preparation of Good Clinical Practice Inspections in Chapter IV of Eudralex Volume 10.

4.5. General Considerations regarding the Schedule for Activities related to GCP Inspections

A model schedule for each step (early activities, initiation, conduct and reporting) is provided in Appendix 4. The times shown in square brackets should be considered as indications and need to be adapted to the respective procedure (e.g. MRP, DCP).

During the MRP a GCP inspection might be requested if a CMS identifies GCP non-compliance relating to the clinical data which may present a risk to public health, which includes issues relating to insufficient data quality. The CMS should communicate the need for a GCP inspection to the RMS by Day 50.

During the DCP, a GCP inspection, where required, should be requested by the RMS as early as possible in the procedure, and normally indicated in the Day 70 Preliminary Assessment Report, but not later than day 105, except in exceptional circumstances, in order to enable the inspection to be conducted in the Day 105 Clock stop period. If a CMS considers an inspection should be carried out they should communicate the need for a GCP inspection to the RMS by Day 100.

If the outcome of the GCP inspection is negative i.e. the study was not conducted in compliance with GCP and a recommendation is included that the data cannot be used in support of a MAA, the RMS in consultation with CMS should consider the necessary actions required in the context of the MAA (e.g. limitations or refusals of the MA and in the case of the MRP whether there is a need for referral in accordance with Directive 2001/83/EC if the product is already authorised in some Member States,). Consequences for other marketing authorizations should be considered.

In case of Type II Variations the need for a GCP inspection should preferably be indicated in the Preliminary Variation Assessment Report to enable the inspection process to take place within the Clock stop period.

4.6. Communication of Inspection Results/Outcomes

For each site inspected, the LI prepares an IR. The IR might be provided to other parties on their reasoned request. Details regarding the exchange of inspection reports are described in the guidance for exchange of GCP inspection reports in Chapter IV of Eudralex Volume 10.

Where applicable, the RI writes an IIR, which is forwarded to the requesting party. The conclusion of the IIR should provide a clear statement on whether the study was conducted in compliance with GCP and should include a recommendation on whether the data can be used in support of a MAA.

The preparation of inspection reports is detailed in the guidance for the preparation of inspections reports in chapter IV of Eudralex Volume 10. The template of the IIR given in the "Procedure for reporting of GCP inspections requested by the EMEA" (INS-GCP-4) may be used as guidance for the preparation of the IIR in the current context.

The IR is sent to the requesting party, as agreed. It is the responsibility of the requesting party (e.g. CMD(h)) to communicate the IR outcome to Member States concerned. For further explanations or a presentation of the overall inspection outcome, the requesting party should contact the RI.

4.7. Consultation with the EMEA GCP Inspection Working Group

The EMEA GCP IWG, in line with the GCP IWG Mandate, should be consulted in case Member Statess, the European Commission, EMEA, Scientific Committees or CMD(h) require expert support on GCP related matters, in particular inspections.

If a Member State, CMD(h) or CHMP considers that the verification of compliance with GCP reveals differences between the Member States involved, they should consult the CMD(h) and GCP IWG. The European Commission may in accordance with Article 15.3 of Directive 2001/20/EC request a new GCP inspection.

4.8. Consultation with the CMD(h)

The Reporting Inspector should communicate a negative outcome (i.e. the study was not conducted in compliance with GCP and a recommendation is included that the data cannot be used in support of a MAA) to the CMD(h) member of the RMS or CMS requesting the inspection. This CMD(h) member should communicate that to the plenary CMD (h) meeting or via the CMD(h) mailbox.

5. RECORDS

The Reporting Inspector arranges for archiving of the IRs of the inspections where he/she took over lead function, the IIR, its appendices and relevant inspection related documents. The LIs archive their IRs and inspection related documents according to the national procedures.

6. COSTS

The inspection fees are covered in accordance with national provisions and requirements.

7. REFERENCES AND RELATED DOCUMENTS

Guidance documents containing the common provisions on the conduct of GCP inspections by competent authorities of the different Member States published on the Eudralex Volume 10.

APPENDIX 1: REQUEST FOR GCP COMPLIANCE EVALUATION AND CLINICAL DATA VERIFICATION

REQUESTING PARTY

Name of institution / authority	Name of contact point /assessor	Telephone / fax / email

PRODUCT / APPLICATION/CLINICAL TRIAL PROTOCOL INFORMATION

Name of Sponsor/Company	Enter name of sponsor and applicant
Name of Finished Product	
Name of Active Substance	
Title of the Clinical Trial	Select one of the key pivotal trials based on the Expert report
Protocol Number	
EudraCT Number	
Phase	
Type of process	e.g. MRP, DCP
CMS countries	
Indication	
Dates when clinical trial was performed	
Other information	

INSPECTION OF THE FOLLOWING SITE(S) IS REQUESTED

Name of site	Address(es) of Sponsor / CRO / Laboratory site(s) to be inspected	Contact point / Investigator	Phone / email

DETAILS ON REASONS/SCOPE FOR INSPECTION

LIST OF SPECIFIC QUESTIONS TO BE EVALUATED DURING INSPECTION

1
2
3
4

OTHER RELEVANT INFORMATION

e.g. on previous inspection results of site / sponsor

APPLICABLE TIMELINES

Target date for the availability of the summary Inspection Report	

Name	
Signature	
Date	

APPENDIX 2: INSPECTOR'S APPOINTMENT FORM

INSPECTION CONCERNED

Name of Sponsor/Company	Enter name of sponsor and applicant
Name of Finished Product	
Name of Active Substance	
Title of the Clinical Trial	

REPORTING INSPECTOR

Name	Address(es)	Institution	Phone / email

For the Appointing Agency

Name	
Signature	
Date	

LEAD INSPECTOR

Name	Address(es)	Institution	Phone / email

For the Appointing Agency

Name	
Signature	
Date	

APPENDIX 3: INSPECTION ENQUIRY FORM

REQUESTING INSPECTORATE

Name of inspectorate	Name of contact point /head inspections unit	Telephone / fax / email

INSPECTION CONCERNED

TYPE OF ACTION REQUESTED

Participation as Lead Inspector	
Participation as Reporting Inspector	
Additional personnel (experts) proposed	

DETAILS ON FINANCIAL REIMBURSEMENT ISSUES

OTHER RELEVANT INFORMATION

Name	
Signature	
Date	

APPENDIX 4: MODEL SCHEDULE OF ACTIVITIES RELATED TO GCP INSPECTIONS

<table>
<tr><td>STEPS OF THE PROCEDURE</td><td colspan="2">TIME ALLOWED</td></tr>
<tr><td>1. Early activities

Request a GCP inspection

Designation of the Reporting Inspectorate

Initial selection of site(s)

Set up of overall time schedule

First contacts to inspectorate(s) concerned

Notification of the inspection to sponsor/applicant</td><td colspan="2">RMS/CMS (or CHMP, in case of a referral according to Directive 2001/83/EC) should determine the time allowed for early activities regarding the request of GCP inspections in MRPs and DCPs.

RMS notifies sponsor/applicant within [10] days after GCP Inspection Request Form signed.

Forwarding of required documents (e.g. Protocol, Clinical Study Report, SOPs etc.), within [10] days after Inspection Request Form signed.</td></tr>
<tr><td>2. Inspection preparation

Notification / announcement of site inspections

Preparation of the inspection plan

Obtaining and reviewing required documents

Finalisation of travel arrangements with the sponsor/applicant</td><td colspan="2">[20] days ✸ after the delivery of the documents requested from the sponsor/applicant to the inspectorates</td></tr>
<tr><td>3. Site inspection</td><td colspan="2">[30] days ✸</td></tr>
<tr><td>4. Writing and circulation of the reports

Writing of the 1st version of the Inspection Report

Reply from the inspectee / party(ies) responsible

Writing of the final version of the Inspection Report

Writing of the IIR and transmission to Requesting Party</td><td>

[15] days ✸

[15] days ✸

[10] days ✸

[10] days ✸</td><td>

Total: [50] days* ✸</td></tr>
</table>

✸Times proposed to complete each step of the initiation; conduct and termination of the inspection are provided in this table. These times, shown in square brackets, should be considered as indications and can be modified if necessary.