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PROCEDURE FOR COORDINATING GCP INSPECTIONS REQUESTED BY THE EMA
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GCP Inspectors Working Group

Applies to: EMA, EU/EEA Inspectorates
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Summary of scope: This procedure describes the different steps of the GCP inspection process and particularly the interfaces between Member States inspection services and CHMP/EMA
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1 INTRODUCTION

Only Good Clinical Practice (GCP) inspections requested by the EMEA are detailed in this procedure.

The legal basis for GCP inspections of medicinal products for which an application for a Marketing Authorisation has been submitted to the EMEA, is to be found in article 57(a)(i) of Regulation (EC) No. 726/2004 which provides that the Agency shall, within its Committees, undertake the following tasks:

- Co-ordination of the scientific evaluation of the quality, safety and efficacy of medicinal products which are subject to Community Marketing Authorisation procedures;
- Co-ordination of the verification of compliance with the principles of good manufacturing practice, good laboratory practice and good clinical practice and the verification of compliance with pharmacovigilance obligations.

One of the criteria for making a decision on an application concerning a medicinal product for human use is the assessment of the clinical documentation. According to the Introduction and general principles of the annex 1 of Directive 2001/83/EC as amended; “All clinical trials, conducted within the European Community, must comply with the requirements of Directive 2001/20/EC of the European Parliament and of the Council 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. To be taken into account during the assessment of an application, clinical trials, conducted outside the European Community, which relate to medicinal products intended to be used in the European Community, shall be designed, implemented and reported on what good clinical practice and ethical principles are concerned, on the basis of principles, which are equivalent to the provisions of Directive 2001/20/EC. They shall be carried out in accordance with the ethical principles that are reflected, for example, in the Declaration of Helsinki”. Therefore the assessment of the clinical documentation may lead to a request for a GCP inspection.

Any clinical trial included in the application could be subject to inspection. This could be a triggered or a routine Inspection (see definitions in 2.2.6 and 2.2.7). Usually, the CHMP request for a GCP inspection is focused on the most important trials involved in the application. The objective of a GCP inspection requested by the CHMP is to:

- Determine whether the trial was conducted in accordance with applicable regulatory requirements which include local regulations and ethical standards, and the CPMP/ICH/135/95 Note for Guidance on GCP, and Directive 2001/83/EC as amended;
- Provide answers to questions arising from the assessment process where it has been determined that these can best be provided through inspection;
- Determine whether the data submitted in the dossier are credible and accurate.

GCP inspections could be triggered for different reasons, for example:

- To verify the GCP compliance statement;
- To examine trials further because of:
 - their importance to the application;
 - the recruitment of subjects from vulnerable groups or other ethical concerns;
 - concerns about the investigational medicinal products;
 - 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.

2 APPLICABILITY OF THIS PROCEDURE AND DEFINITION OF TERMS

2.1 Inspectorates and Inspectors to whom this procedure applies

For the purpose of this procedure the following inspectorates may be involved:

- From all EU/EEA countries where sites are to be inspected
- From the same country as the CHMP Rapporteur/Co-Rapporteur
- From other EU/EEA countries if needed

The Inspectors performing the tasks and duties described in this procedure are appointed by the inspectorates involved. The process of designating the inspectorates involved is described in sections 3.1.3 and 3.1.4.

2.2 Definition of terms

2.2.1 Reporting Inspectorate

The Inspectorate from an EU/EEA State requested and accepting to designate the Reporting Inspector.

2.2.2 Reporting Inspector

The Inspector designated by the Reporting Inspectorate to co-ordinate the preparation of the inspection, the conduct of the inspection, and the activities of the inspectors.

The Reporting inspector has the following general duties:

- co-ordinating the
 - preparation of the inspection
 - practicalities of the inspection (with the inspectors and the sponsor/applicant)
 - conduct of the inspection
 - preparation of the reports by the inspectors involved
- checking that the timelines for the inspection are kept
- writing and co-signing the Integrated Inspection Report (IIR)
- acting as the main communication point between the inspection team and the EMEA Inspection Sector. The Reporting Inspector and the EMEA Inspection Sector are responsible for the communication between the inspectorates and inspectors involved, the Rapporteur/Co-Rapporteur and the CHMP. The system of communication should however be flexible and there can be direct communication between the involved parties, including the assessors, where this is more practical
- management of the live central archive related to the GCP inspection
- the Reporting Inspector may also be the Lead Inspector (see below) for one or more sites.

2.2.3 Lead Inspector

The Inspector who has the following duties for the GCP inspection of at least one inspection site:

- evaluation of the feasibility of the inspection as requested and discussion with the Reporting Inspector
- organisation of the practicalities of the inspection, with the inspectee,
- leading the conduct of the inspection on site,
- communication between the inspectee and the Reporting Inspector/EMEA Inspection Sector. The system of communication should however be flexible and there can be direct communication between the involved parties where this is more practical
- writing and signing the Inspection Report
- reviewing and co-signing the Integrated Inspection Report
- Entering in EudraCT the data for the inspected site

2.2.4 Inspection Report (IR)

An Inspection Report (IR) is prepared for each site inspected. The Inspection Report will be written in English, unless required by local regulations to be in local language. In the latter case the Inspection Report will be translated to English under the responsibility of the Lead Inspector. The inspection report is signed by the Lead Inspector and other inspectors as required by local legal requirements and SOPs.

2.2.5 Integrated Inspection Report (IIR)

For each GCP inspection request made by the CHMP one IIR is prepared (see procedure INS/GCP/4). This report is in English, and summarises the critical and major findings of the inspection identified at all involved sites. The report contains an evaluation of the quality of the submitted data and of the compliance with the GCP principles based on the findings from all inspected sites. It is written and signed by the Reporting Inspector, and reviewed and signed by the Lead Inspectors. The IRs are attached to the IIR as appendices. Each inspector should nominate a proxy who may sign on their behalf or agree with the Reporting Inspector that the latter may sign on their behalf, if they are not available when the report has to be signed. Signature may be obtained by fax, and the originals mailed to the Reporting Inspector. Where there is only one site inspected the IIR and IR can be a single document provided that they are in English and a summary of the findings and conclusion is given – the report should fulfil the objectives of both, the IIR and the IR.

2.2.6 Triggered inspection

This is an inspection requested because there is a concern due to either the actual issues observed or the potential impact of deviations from GCP on the conduct of the study as a whole or at a particular site. In addition products with a major impact factor could be considered to require special attention.

2.2.7 Routine inspection

Routine inspections are inspections carried out as a routine surveillance of GCP compliance, in the absence of specific trigger elements. These routine inspections should have a random element in that not all applications would necessarily give rise to a GCP inspection, however the applications, clinical trials and sites should be selected based on a set of criteria to ensure that a range of different situations are covered (e.g. origin of pivotal data, target population, type of product etc). Such inspection will usually be requested earlier, during the first phase of assessment and before the adoption of the List of Questions.

3 STEPS OF THE PROCEDURE

Times allowed to complete each step of the initiation, conduct and termination of the inspection are provided below. These times, shown in square brackets, should be considered as indications and can be modified if necessary. The inspection process will be integrated into the assessment process. Appendix 1 contains process maps illustrating the designation of the Reporting and Lead Inspectorates/Inspectors. Appendix 2 contains a tabular presentation of the time intervals involved for different steps of the inspection process. The timelines for practicalities e.g. discussion of findings and conclusions (including the possibility of a teleconference between the inspection team members), forwarding of the IRs to the Reporting Inspector and signing of the reports, should be established by the inspection team prior to the inspection for each IR and for the IIR.

3.1 Early activities of EMEA and CHMP representatives in developing a request

EMEA and CHMP should determine the time allowed for this step.

3.1.1 Preparation and adoption of the inspection request

At any time after the validation of the application the Rapporteur and Co-Rapporteur or other CHMP delegation may signal that in their opinion a GCP inspection is necessary or the EMEA inspection sector may propose to the (Co-)Rapporteurs a routine inspection of an application based in a set of predefined criteria. The selection of sites to be inspected and the determination of the scope of the inspection are made by communication between the Rapporteur/Co-Rapporteur (and their assessors), and the EMEA inspection sector. The selection of sites and scope of the inspection may be further refined by discussion with the potential inspectorates/inspectors.

The request should be made to the CHMP using the applicable GCP Inspection Request Form. The EMEA Head of Inspection Sector sign the request. This request should clearly state 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 any other issues relevant to the inspection. Where the CHMP considers that a GCP inspection is appropriate, for the assessment of the application or for routine purposes, the CHMP adopts the request.

3.1.2 Communication of the inspection request

After the adoption by the CHMP, the request is forwarded to the EMEA Inspection Sector for co-ordination.

3.1.3 Designation of the Reporting Inspectorate

A contact point for the purpose of deciding on the availability of the inspectorate to perform an inspection is appointed by each Member State Inspectorate(s) and notified to the EMEA.

One EU/EEA Inspectorate is designated as the “Reporting Inspectorate”. In general, the Reporting Inspectorate should be from the same country as the CHMP Rapporteur or Co-Rapporteur. However, if for any reason, the Inspectorate first designated cannot fulfil this task, the EMEA Inspection Sector should determine the availability of other Inspectorates and designate another Reporting Inspectorate.

The EMEA designates the Reporting Inspectorate according to the following sequence, subject to the availability of inspector(s):

- Rapporteur
- Co-Rapporteur
- Member State with the highest number of sites to be inspected
- Member State with next highest number of sites to be inspected and so on in descending order of number of sites
- Other Member States

Where the site(s) to be inspected are located in a single EU/EEA state (or small number (3 or less) of EU/EEA states), that Inspectorate is usually designated as the Reporting Inspectorate (that being the state with the most sites to be inspected or the first to accept the role). The Rapporteur or Co-Rapporteur inspectorate may choose to participate in the inspection team.

The EMEA sends the request for participation of the reporting inspectorate to the relevant Member States and designates the Reporting Inspectorate on the basis of responses received within 5 working days.

Where there are sites in EU/EEA Member States, the inspectorate in each of these is requested to act as lead inspector for the sites in their country. If an inspectorate wishes to request the assistance of another inspectorate they indicate this to the EMEA within 5 working days.

The CHMP adopted inspection request is sent simultaneously to the contact person in each Member State for information, and indication of potential availability to participate in the inspection team. Member States may send trainees, subject to considerations of the size of the inspection team. Such trainee participation will not give rise to a share of the inspection fee.

The Member State inspectorate which undertakes the Reporting Inspectorate role ensures effective communication with the Rapporteur, Co-Rapporteur and the relevant assessors.

3.1.4 Designation of the inspection team

EMEA Inspection Sector checks the availability of GCP Inspectorates in EU/EEA, which are invited to conduct the requested inspection. When it is not feasible for an Inspectorate to carry out the requested parts of the inspection, the competent authority of that country may ask, in co-ordination with the EMEA, another Inspectorate to conduct the inspection (this will be in accordance with local or national legislation where sites are located in EEA).

Each Inspectorate concerned by the inspection is in charge of the designation of at least one appropriately qualified inspector to be part of the inspection team.

For each selected site, one Lead Inspector should be designated (this may be the same or different people for the different sites selected).

3.1.4.a) GCP inspections in EU/EEA countries

Where the inspection site is located in the EU/EEA the Lead Inspector will be from the Inspectorate in the country where the site(s) to be inspected is located. There is routinely one Lead Inspector for any given site inspection.

3.1.4.b) GCP inspections in third countries

For inspection in third countries the Reporting Inspector, and/or other inspectors from EU/EEA States may act as Lead Inspector.

The EMEA will contact local authorities in third countries as appropriate.

3.1.5 Communication of the Inspection Request to the Reporting and Lead Inspectorates and contract for the inspection

The inspection request is communicated to the Reporting Inspectorate and Lead Inspectorates by the EMEA. They are also informed of any GXP inspections requested for the same application.

The EMEA prepares the contract for the inspection in accordance with the Article 62(3) of Council Regulation (EC) No 726/2004, and other relevant procedures.

3.1.6 Announcement of the inspection to the applicant

The EMEA notifies the applicant, in accordance with the EMEA SOPs, that an inspection has been requested, using a standard letter. In the announcement letter the applicant is requested to confirm in writing that the sites accept to be inspected and that they will make all required documents available, for direct access by the inspectors. The applicant is also requested in this letter to prepare copies of an initial set of documents for provision to the inspectors, the inspectors can then supplement this list with additional requests to the applicant. The EMEA is responsible for arranging further communication, between inspectorates and the applicant.

3.2 Inspection preparation: [20] days

Each Inspectorate concerned is in charge of the designation of at least one appropriately qualified inspector to be part of the inspection team, who can act as Lead Inspector.

3.2.1 Technical preparation

The technical preparation of the inspection is detailed in a separate procedure INS/GCP/2.

Concerned Inspectorates should participate in the discussion about the feasibility of the inspection as requested and the time schedule.

Any change in the sites selected for inspection should be adopted by the CHMP.

3.2.2 Co-ordination of travel and accommodation arrangements.

The inspection team makes contact directly with the applicant, who is requested to make the appropriate arrangements on behalf of the inspection team.

3.3 Site inspection: [30] days

During this period inspections are conducted at different sites. The conduct of the inspection is described in a separate document (INS/GCP/3) with appendices by type of site.

3.4 Writing and circulation of inspection reports: [50] days

The preparation of inspection reports is detailed in a separate procedure INS/GCP/4.

The Inspection Request will make clear the status of the evaluation timeline at the time of adoption of the request.

The letter announcing the inspection to the applicant, from EMEA, will make clear that any responses to the issues raised by the inspection must be addressed by the applicant to each member of the inspection team, in addition to Rapporteur/Co-Rapporteur, CHMP, and EMEA PTL (Product Team Leader) and Inspection Coordinator. This in particular means any responses submitted as part of a response to a LoQ or LOI, and/or any written comments related to the inspection, GCP compliance and/or validity of the data.

During the conduct of the inspection or preparation of the reports the inspectors may decide to provide particular relevant findings, in advance of the circulation of the inspection reports. This is to provide advance warning of particular problem issues. These findings that might influence the acceptance/non-acceptance of the trial data should be reported as early as possible during the preparation of the different reports by the Lead Inspector to the Reporting Inspector and by the Reporting Inspector to the EMEA Inspection Sector. The EMEA Inspection sector will inform the Rapporteur/Co-Rapporteur and CHMP as appropriate.

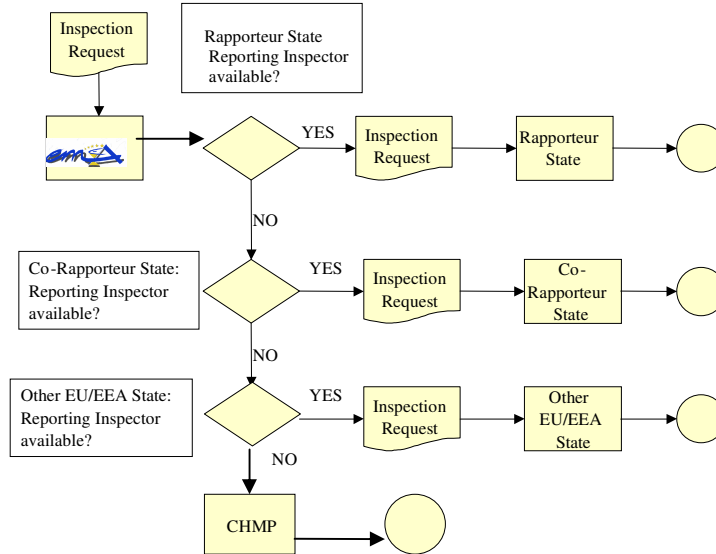
For each site inspected, the Lead Inspector prepares an Inspection Report (IR).

The Reporting Inspector writes an Integrated Inspection Report (IIR) providing an overall summary, which is forwarded to the EMEA Inspection Sector. The EMEA inspection sector forwards the report after review and acceptance to the Rapporteur/Co-Rapporteur and CHMP.

Appendix 1: Process Maps for the Designation of Inspectorates and Inspectors involved

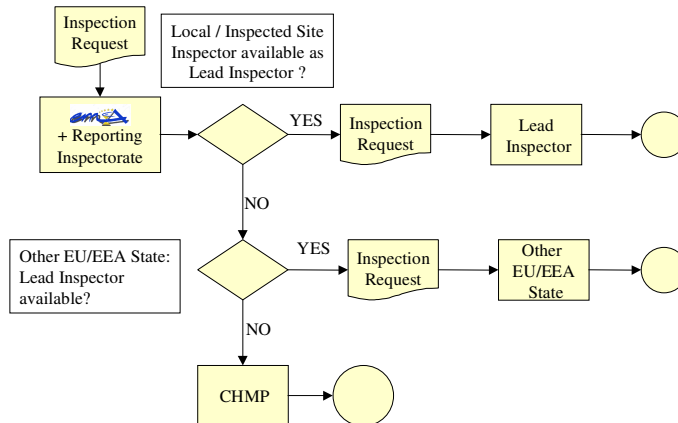
- **Reporting Inspectorate**
- **Lead Inspectorates (sites in EU/EEA Countries)**
- **Lead Inspectorates (sites in Third Countries)**

Process Map: Decision Tree GCP Reporting Inspector Selection *

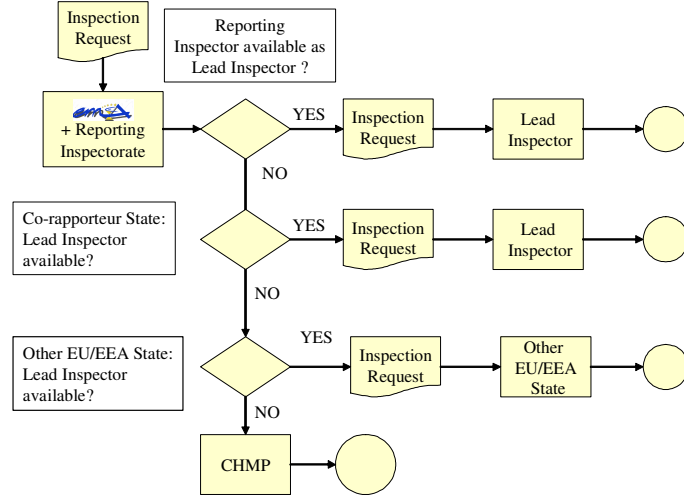


* See section 3.1.3 where inspected sites are in 3 or less EU/EEA member states only

Process Map: Decision Tree GCP Lead Inspector Selection for Inspection in EU/EEA Country



Process Map: Decision Tree GCP Lead Inspector Selection for Inspection in Third Country



Appendix 2:

Table of process steps and projected time intervals for these

**ACTIVITIES RELATED TO GCP INSPECTIONS REQUESTED BY CHMP:
INDICATIVE * TIME SCHEDULE**

STEPS OF THE PROCEDURE	TIME ALLOWED	
1. Early activities of EMEA / CHMP Request for a GCP inspection Initial selection of sites Set up of overall time schedule Designation of the Reporting and other Inspectorates First contacts EMEA / Inspectorates concerned Notification of the inspection to applicant	To be determined by EMEA/CHMP Notify applicant within [10] days of CHMP meeting Notify Reporting inspectorate and other inspectorate(s) within [10] days of CHMP meeting Forwarding of required documents, (LOQs, CSR, protocol, etc) within [10] days of CHMP meeting	
2. Inspection preparation Notification / announcement of site inspections Preparation of the inspection plan Obtaining and reviewing required documents Finalisation of travel arrangements with the applicant	[20] days * after the delivery of the documents requested from the applicant to the inspectorates	
3. Site inspection	[30] days *	
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 and of the SIR Writing of the IIR and transmission to EMEA/CHMP	[15] days * [15] days * [10] days * [10] days *	Total: [50] days* *
5. Review of the reports by EMEA for adherence to applicable reference texts and EMEA guidelines.	[5] days *	

Note: the numbers in brackets refer to calendar days

*Times allowed 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.

* The EMEA should be notified as soon as possible by the Reporting Inspector of any relevant finding that may influence the acceptance / non acceptance of the trial data.

**Appendix 3: References and list of documents used in the preparation of
this Procedure**

References:

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