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Procedure for coordinating GCP inspections requested by the CHMP

GCP Inspectors Working Group

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1. Summary of scope

This procedure describes the different steps of the Good Clinical Practice (GCP) inspection process and particularly the interfaces between Member States inspection services and the Committee for Medicinal Products for Human Use (CHMP)/European Medicines Agency (EMA).

2. Introduction

Only GCP inspections requested by the CHMP 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 Agency, 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 EU 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; “All clinical trials, conducted within the European Union, 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 Union, which relate to medicinal products intended to be used in the European Union, 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 ‘for cause’ or a routine inspection (see definitions in 3.2.6 and 3.2.7). 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;
- 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 (refer to "Points to consider for assessors, inspectors and EMA inspection coordinators on the identification of triggers for the selection of applications for "routine" and/or "for cause" inspections, their investigation and scope of such inspections").

3. Applicability of this procedure and definition of terms

3.1. 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 4.1.3 and 4.1.4.

3.2. Definition of terms

3.2.1. Reporting inspectorate

The reporting inspectorate is the inspectorate from an EU/EEA state requested and accepting to designate the reporting inspector.

3.2.2. 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 duties:

- to co-ordinate 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;
- to prepare the cumulative preliminary outcome report and send it to the rapporteur/co-rapporteur; (refer to INS-GCP-4 for the template);
- to check that the timelines for the inspection are kept;
- to write and to sign the integrated inspection report (IIR); (refer to INS-GCP-4 for the template);
- to act as the main communication point between the inspection team and the EMA Compliance and Inspections department.

The reporting inspector and the EMA Compliance and Inspections department 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:

- To liaise when necessary, with the rapporteur/co-rapporteur and sign the joint inspection assessment (JIA) document, which will constitute an addendum to the IIR.
- To manage 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.

3.2.3. Lead Inspector

The lead inspector is the inspector, who has the following duties for the GCP inspection of at least one inspection site:

- evaluating the feasibility of the inspection as requested and discussion with the reporting inspector;
- organising the practicalities of the inspection, with the inspectee;
- leading the conduct of the inspection on site;
- ensuring communication between the inspectee and the reporting inspector/Compliance and Inspections department. The system of communication should however be flexible and there can be direct communication between the involved parties where this is more practical;
- preparing the preliminary outcome report and sending it to the reporting inspector;
- writing and signing the inspection report;
- reviewing and signing the integrated inspection report;
- signing, when applicable, the JIA; (refer to INS-GCP-4);
- entering in EudraCT the data for the inspected site.

3.2.4. 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.

3.2.5. Integrated inspection report (IIR)

For each GCP inspection request made by the CHMP, one IIR is prepared (refer to 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 and ethical standards 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 his/her behalf or agree with the reporting inspector, that the latter may sign on his/her behalf, if he/she is not available when the report has to be signed. Signatures may be scanned images to a PDF document. Where there is only one site inspected the IIR and IR can be a single document provided that it is 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.

In cases where the GCP inspection has identified issues which potentially impact the validity of data and thus the benefit-risk evaluation or the evaluation of the overall ethical conduct of the trial(s), the inspectors should indicate in the IIR the need for a JIA.

The rapporteur/co-rapporteur should liaise with the reporting and lead inspectors to discuss findings that are identified by either party as possibly impacting the validity of data and consequently on benefit-risk evaluation or major issues regarding ethics and/or patient safety. E-mail exchanges may suffice and if necessary a teleconference should be arranged with Compliance and Inspections department support. A summary on the discussion of the findings and the opinions expressed by the inspectors and rapporteur/co-rapporteur should be described in the JIA.

The JIA should be drafted by the rapporteur and agreed by the co-rapporteur, the reporting and lead inspectors. All parties should sign and date it. The JIA should be concise and readable as a stand-alone entity that can be copied and pasted in its entirety into the centralised procedure assessment report (refer to procedure INS-GCP-4 for further details).

3.2.6. For cause 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 (refer to "Points to consider for assessors, inspectors and EMA inspection coordinators on the identification of triggers for the selection of applications for "routine" and/or "for cause" inspections, their investigation and scope of such inspections").

3.2.7. 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.), (refer to "Points to consider for assessors, inspectors and EMA inspection coordinators on the identification of triggers for the selection of applications for "routine" and/or "for cause" inspections, their investigation and scope of such inspections"). Such inspections will usually be requested earlier, during the first phase of assessment (day 30 or day 60 of the assessment procedure) and before the adoption of the List of Questions.

4. Steps of the procedure

The 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.

4.1. Early activities of EMA and CHMP representatives in developing a request

The Compliance and Inspections department and CHMP should determine the time allowed for this step.

4.1.1. 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 Compliance and Inspections department may propose to the (co-)rapporteurs a routine inspection of an application based on 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 Compliance and Inspections department. 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 head of the Clinical and non-Clinical Compliance service signs 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.

The deadline for the provision of the IIR will be set out in the inspection request and will be two weeks before the CHMP week and no later than two weeks before day 150. This will sometimes not be possible, especially for triggered inspections. In all cases the final IIR (with JIA addendum if required) should be available in time to be addressed in the day 180 list of outstanding issues (LoOI). The target time line for submission of the IIR if a JIA addendum will be needed is two weeks before day 180.

4.1.2. Communication of the inspection request

After the adoption by the CHMP, the request is forwarded to the Compliance and Inspections department for co-ordination.

4.1.3. 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 Agency.

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. For routine GCP inspections, the reporting inspectorate will be designated by the Compliance and Inspections department according to the following sequence, subject to the availability of inspector(s) or unless otherwise agreed:

- rapporteur or co-rapporteur;
- other EU Member States.

For 'for cause' inspections, the reporting inspector should come from the inspectorate of the rapporteur or co-rapporteur country.

The member state inspectorate which undertakes the reporting inspectorate role, should preferably participate in all site inspections. If this is not possible then it should participate at least in one site inspection and with the agreement of the inspection team. The reporting inspectorate should ensure effective communication with the rapporteur, co-rapporteur and the relevant assessors.

4.1.4. Designation of the inspection team

The Compliance and Inspections department checks the availability of GCP inspectorates in the 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 EMA, another inspectorate to conduct or assist in the inspection (this will be in accordance with national legislation where sites are located in the EU/EEA).

For 'for cause' inspections, the inspection team should preferably include the inspectorate of the rapporteur or co-rapporteur country.

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). In accordance with Article 15(1) of Directive 2001/20/EC the inspections shall be carried out on behalf of the Community and the results shall be recognized by all the other Member States.

GCP inspections in EU/EEA countries

Inspections of sites located within the EU/EEA will normally be joint inspections i.e. inspectorates from two different MS. However, upon agreement amongst the concerned inspectorates and the Compliance and Inspections department, inspections could be carried out, under exceptional circumstances, only by the inspectorate of the MS in which the site is located.

GCP inspections in countries located outside the EU/EEA

The inspection of the sites located outside the EU/EEA will usually be conducted by two inspectorates one or both of which may also have been involved in any EU/EEA based site inspection for the same requested inspection. The reporting inspector, and/or other inspectors from EU/EEA States may act as lead inspector.

Number of inspectors per inspection team

The inspection team should preferably consist of two inspectors (lead inspector and supporting inspector) per inspection request and site inspected. One additional team member may be involved in

the following situations (more than that shall be properly justified and in particular for site inspections in countries located outside the EU/EEA):

A) At the request of the reporting inspector:

A1) When one or more of the following circumstances concur:

- complexity of the trial,
- more than one trial to be inspected,
- high number of patients recruited per site and in particular for sites outside the EU/EEA,
- multiple sites to be inspected in different parts of the world,
- urgent inspection request that requires the inspections to be conducted and reported in a short timeframe,
- experience of the inspectors involved in EMA inspections,
- specific language skills required e.g. for inspections outside the EU/EEA.

A2) When the involvement of an expert with appropriate qualifications is considered necessary. When possible this expert shall be preferably from the MS of one of the two inspectors involved in the inspection in order to avoid more than two MS involved in one inspection request.

A3) When the reporting inspector cannot be involved in all the sites inspected and therefore prefers one inspector from his/her MS/National Competent Authority (NCA) to follow up the inspection in the other sites (for sites outside the EU/EEA). In this particular case only two inspectors per site is expected.

In all the above situations the final team for the whole inspection, shall preferably be from only two different inspectorates unless section A2) applies.

B) At the request of the lead inspector, with agreement of the reporting inspector and only for EU/EEA site inspections:

This section B) does not apply for site inspections outside the EU/EEA:

B1) When the lead inspector wants to involve another inspector from his/her MS in order to gain more experience in CHMP requested inspections.

B2) When the lead inspector considers there is room to involve another inspector from his/her MS or a different MS for training purposes. This inspector will act as an observer trainee and not as an inspector for that concerned inspection. Such trainee participation will not give rise to a share of the inspection fee.

In both cases more than 3 inspectors per site shall be avoided unless it is considered necessary and is well justified.

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

Communication of the Inspection Request to the Reporting and Lead Inspectorates

The inspection request and template reports to be used are communicated to the reporting inspectorate and lead inspectorates by the Compliance and Inspections department. They are also informed of any GXP inspections requested for the same application.

Announcement of the inspection to the applicant

The Compliance and Inspections department notifies the applicant, in accordance with the Agency 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, who can then supplement this list with additional requests to the applicant. The format of the documents (paper, electronic) can be discussed/decided by the reporting inspector. The Compliance and Inspections department is responsible for arranging further communication between inspectorates and the applicant.

The letter announcing the inspection to the applicant, from the Compliance and Inspections department, 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 the rapporteur/co-rapporteur, CHMP, and Agency Product Team Leader (PTL) and Compliance and Inspections department. This in particular means any responses submitted as part of a response to a List of Questions (LoQ) or LoOI, and/or any written comments related to the inspection, GCP compliance and/or validity of the data.

4.2. 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.

4.2.1. Technical preparation

The technical preparation of the inspection is detailed in a separate procedure (refer to 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.

4.2.2. Co-ordination of travel and accommodation arrangements

The inspectors make contact directly with the applicant, who is requested to make the appropriate arrangements, as per inspectors' national procedures.

4.3. Site inspection [30] days

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

Following the inspections, the reporting inspector should submit a cumulative preliminary outcome report based on the preliminary outcome reports received from the lead inspectors. This should be submitted to the rapporteurs/co-rapporteur. In case of a negative preliminary outcome, communication between the reporting inspector, the rapporteur and co-rapporteur should take place with support from the Compliance and Inspections department (refer to procedure INS-GCP-4 for further details).

4.4. Writing and circulation of inspection reports: [50] days

The preparation of inspection reports is detailed in a separate procedure (refer to INS-GCP-4).

The inspection request will make clear the status of the evaluation timeline at the time of adoption of the request (section 4.1.1).

For each site inspected, the lead inspector prepares an IR.

The reporting inspector writes an IIR providing an overall summary, which is forwarded to the Compliance and Inspections department. The Compliance and Inspections department forwards the report after review and acceptance to the rapporteur/co-rapporteur and CHMP. Once the IIR has been circulated to the CHMP, the Compliance and Inspections department circulates the IIR with all the appendices to the applicant.

Since the target time line for submission of the IIR is two weeks before the CHMP meeting and no later than two weeks before day 150, in cases where a JIA is required, there will be at least one week allowed for establishing the interaction between inspectors and the rapporteurs and preparing the JIA.

The JIA will be finalised and added as an addendum to the IIR in the week before the CHMP. This will allow the CHMP to take it into consideration prior to day 150. This will sometimes not be feasible, especially for triggered inspections, but all efforts should be made where possible to communicate to the rapporteur/co-rapporteur at least those GCP findings (preliminary or otherwise), that could have an impact on benefit-risk evaluation or serious ethical misconduct. If the necessary information is not available in time, then a holding question should be included in the LoOI as appropriate. In all cases the final IIR (with JIA addendum if required) should be available in time to be addressed in the responses to the day 180 LoOI. The target time line for submission of the IIR - if a JIA appendix will be needed, is two weeks before day 180 when the assessment procedure restarts.

The final IIR, including the JIA, will be circulated to the CHMP by the Compliance and Inspections department and to the PDCO for inspections of paediatric clinical trials.

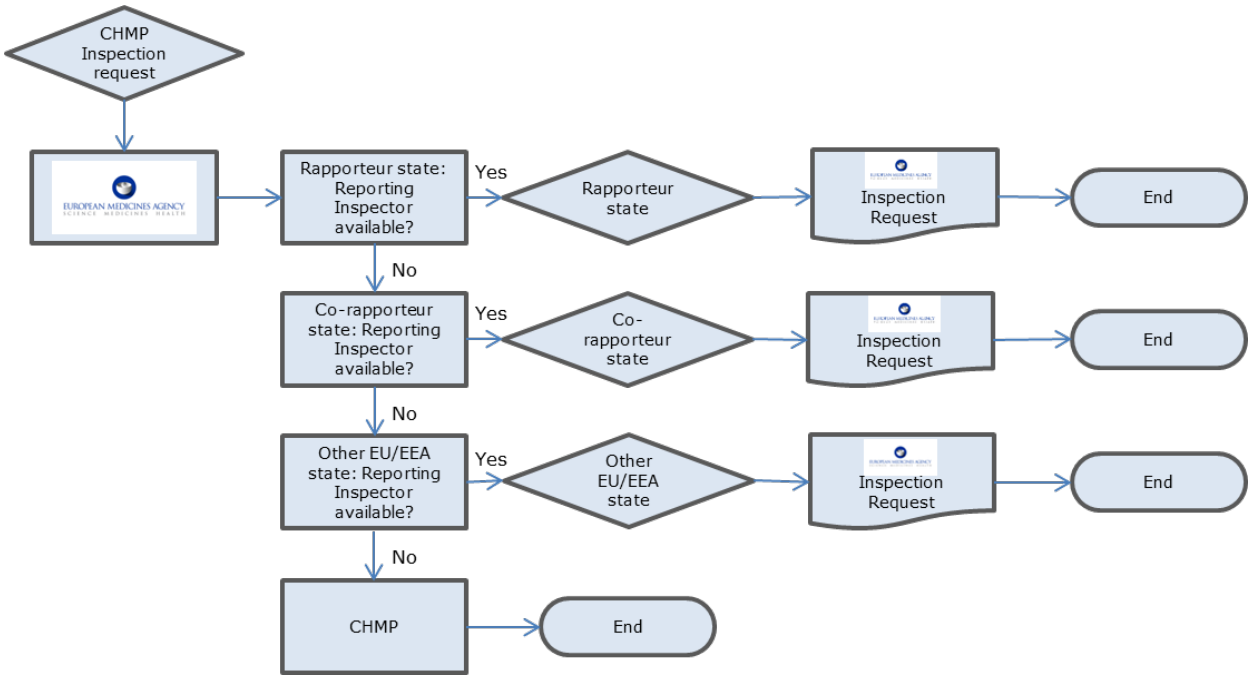
5. Appendices

5.1. Appendix 1: Process maps for the designation of inspectorates and inspectors involved

- Reporting inspectorate for “for cause” inspections.
- Lead inspectorates (sites in EU/EEA countries).
- Lead inspectorates (sites in third countries).

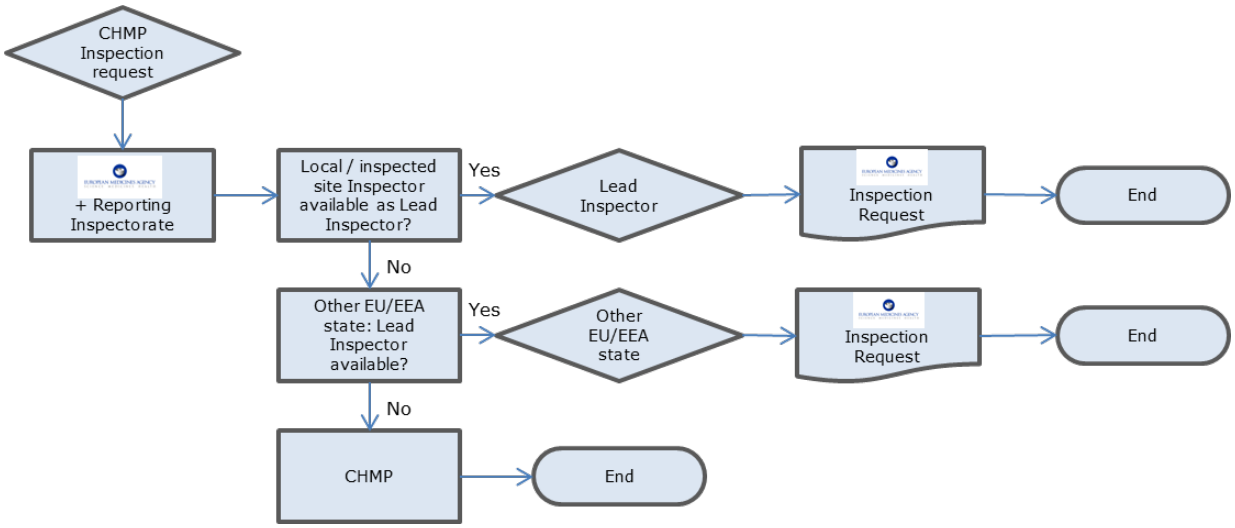
Process Map:

Decision tree for selection of GCP Reporting Inspector



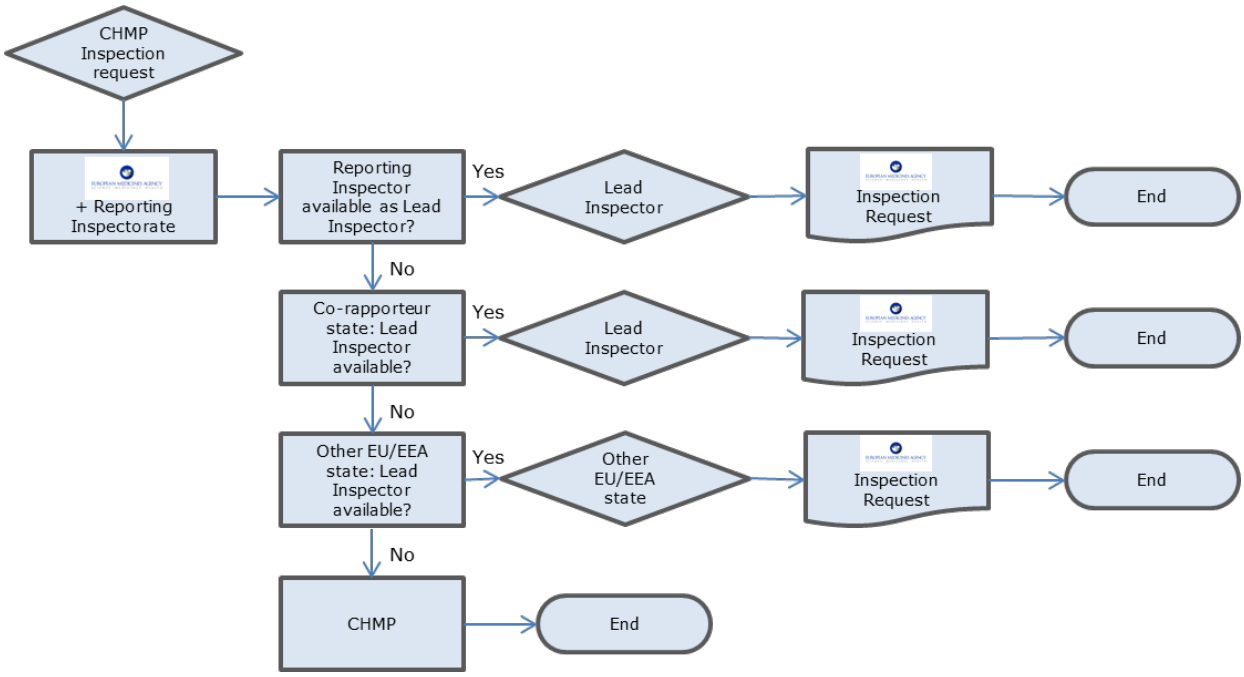
Process Map:

Decision tree for selection of GCP Lead Inspector for Inspection in EU/EEA Country



Process Map:

Decision tree for selection of GCP Lead Inspector for Inspection in Third Country



5.2. Appendix 2:

Table of process steps and their projected time intervals

Table 1. Activities related to GCP inspections requested by CHMP: indicative* time schedule

STEPS OF THE PROCEDURE	TIME ALLOWED
1. Early activities of Compliance and Inspections department/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 Compliance and Inspections department/inspectorates concerned; • notification of the inspection to applicant.	To be determined by Compliance and Inspections department/CHMP
	Notify applicant and request necessary documents for inspection preparation within 10 working days of CHMP meeting. Applicant to respond within 10 working days of the announcement of the inspection, or otherwise agreed with the reporting inspector. Notify reporting inspectorate and other inspectorate(s) within 10 working 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 inspection report;	[15] days*
• responses from the inspectee/party(ies) responsible;	[15] days*
• writing addendum of the inspection report – evaluation of responses;	[10] days*

STEPS OF THE PROCEDURE	TIME ALLOWED
• writing of the IIR and transmission to Compliance and Inspections department/CHMP.	[10] days*
	Total: [50] days*
5. Review of the reports by Compliance and Inspections department for adherence to applicable reference texts and procedures	[5] days*
6. Review and Approval of JIA by reporting and lead inspectors (when applicable)	[5] days*, in the week before the CHMP.

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.

5.3. 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" and "Procedure for Reporting GCP Inspections requested by the CHMP"