EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

7 March 2018
EMA/431276/2016

Guidance for coordination of GCP inspections requested in the context of marketing authorisation applications for mutual recognition and decentralised procedures and cooperation between Member States

Adopted by GCP Inspectors Working Group (GCP IWG)	4 September 2017
Adopted by the Coordination Group for Mutual Recognition and Decentralised Procedure – Human (CMD(h))	24 January 2018

Keywords	***Coordination of GCP inspections***

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Guidance for coordination of GCP inspections requested in the context of marketing authorisation applications for mutual recognition and decentralised procedures and cooperation between Member States

Table of contents

Abbreviations

BE/BA - bioequivalence/bioavailability

CHMP - Committee for Medicinal Products for Human Use

CMDh - Coordination Group for Mutual Recognition and Decentralised Procedure – Human

CMDh GCP WP - Coordination Group for Mutual Recognition and Decentralised Procedure (human) Good Clinical Practice Working Party

CMS - concerned Member State

DCP - decentralised procedure

EMA - European Medicines Agency

EU/EEA - European Union/European Economic Area

EU CT system - European Union clinical trial system

GCP **-** good clinical practice

GCP IWG - GCP Inspectors Working Group

IR - inspection report

LI - lead inspector

MAA - marketing authorisation application

MRP - mutual recognition procedure

NCA - national competent authority

RI - reporting inspectorate

RMS - reference Member State

SIO - summary inspection outcome

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 Member States (RMS) and concerned Member States (CMS) and the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) in the context of the evaluation of GCP compliance of marketing authorisation applications (MAAs) in the mutual recognition procedure (MRP) and decentralised procedure (DCP). The guidance covers GCP inspections (especially bioequivalence/bioavailability BE/BA) to be carried out by the competent authorities of Member States in the context of the MRP and DCP.

The scope of this guidance document is to harmonise the conduct of inspections by the competent authorities of the different Member States (MSs), this is in line with article 9 of the Commission Implementing Regulation on the detailed arrangements for the good clinical practice inspection procedures pursuant to Regulation (EU) No 536/2014 of the European Parliament and of the Council (Commission Implementing Regulation (EU) 2017/556) which provides for the development and improvement of commonly recognised standards of GCP inspections by MSs in collaboration with the Commission and the European Medicines Agency. Any clinical trials conducted within the EU/EEA as well as clinical trials conducted outside the EU/EEA which relate to medicinal products whose application is under evaluation or that 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. provisions of Regulation (EU) No 536/2014, Commission Implementing Regulation (EU) No 2017/556, Directive 2001/83/EC as amended by Directive 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 (EMA/839541/2015) is published in Chapter IV of Eudralex Volume 10.

2. Scope

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

3. Responsibilities

3.1. Requesting party

The following parties may request GCP inspections in above-mentioned context and are referred to as the "requesting party":

- CMDh;
- National competent authority (**NCA**) either reference Member State (RMS) or concerned Member State (CMS).

This guidance should be followed when there is a referral in accordance with Directive 2001/83/EC unless the requesting party is the CHMP (Committee for Medicinal Products for Human Use). In those cases where the inspection is specifically requested by the CHMP, the "Procedure for coordinating GCP inspections requested by the CHMP" (EMA/INS/GCP/55482/2013) should be followed.

3.2. Reporting inspectorate (RI)

The reporting inspectorate 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 inspection result. As outlined in article 78 of the Regulation (EC) No 536/2014 inspections shall be conducted under the responsibility of the Member State where the inspection takes place. Where an inspection is required for an MRP or DCP the inspectorate of the RMS should assume the task of the RI. The RI assigns the reporting inspector. 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 (if applicable).

In this case the RMS inspectorate may participate as a co-inspectorate.

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.

For CHMP referrals, the inspectorate of the rapporteur or co-rapporteur Member State 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 CHMP" If the CHMP is not the requesting party, then the above criteria will apply.

3.3. Reporting inspector

The responsibilities of the reporting inspector are set out in the guidance relating to the preparation of GCP inspections (EMA/165056/2016) 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:

- to assemble the inspection team;
- to distribute the inspection request form (Appendix 1);
- to write and sign the summary of inspection outcome (SIO);
- to act as the main communication point between the inspection team and the involved parties i.e. sponsor, applicant, NCA, RMS, CMS, CMDh, the GCP Inspectors Working Group (GCP IWG)/CMDh GCP WP, and in case of a referral, CHMP, EMA.

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 EudraLex Volume 10. The LI has also the following general duties:

- To review and co-sign the SIO if applicable;
- To enter the details of the inspection in the EU CT system, in line with the procedure for the standardization of entries in EU CT system;
- To inform the third countries regulatory authorities when sites in third 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 inspection (EMA/165056/2016) reports in Chapter IV of EudraLex Volume 10.

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.

Once finalised, the IR will be submitted to the EU portal and Database as required by Article 78(6) of Regulation (EU) No 536/2014.

3.6. Summary of inspection outcome (SIO)

The SIO is only relevant when more than one site was inspected and more than one IR issued. 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 SIO. The SIO 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 SIO conclusions should recommend any follow-up to be requested from the applicant or a further inspection if considered necessary.

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 reliable and robust;
- to examine clinical trials further because of, e.g.:
  - their importance in 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,
  - external allegations of misconduct.
  - The principles detailed in the guidance document on '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' (EMA/INS/GCP/167386/2012) can also be considered for the selection of marketing authorisation applications (MAAs) to be part of a programme of routine inspections and of potential triggers at the different stages of the assessment process.
  - With regards to bioequivalence clinical trials, the guidance on triggers for inspections of bioequivalence trials (EMA/7886/2016) further details specific aspects to be considered by assessors in deciding on the need for a trigger GCP inspection of bioequivalence studies.

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.

The initial contact point for the requesting party is the potential RI. After his/her appointment (see section 3.2), the timeline for the conduct of the inspection and the availability of the IR/SIO 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 GCP inspection results are available in the EU CT system or any GXP inspections are requested for the same application, trial, organisation(s), institution(s) or facility/ies.

After receiving the draft inspection request from the assessor, the RI communicates the draft timelines and other relevant issues to the relevant inspectorates and gives feedback to the requesting party.

4.2. Designation of the inspection team

An inspection team should consist of at least two inspectors or of one inspector and one expert. 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 a 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.

The RI(s) or LI(s) may appoint additional 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 or observers, 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.

4.3. Communication of the inspection request to the reporting and lead inspectorates and appointment of inspectors

This follows the national procedures in place in each member states.

At this point in time the inspection will be announced to the sponsor and applicant, in case they are not the same, by the RMS, but inspections might also be performed without announcement. Detailed information is given in the guidance for the preparation of good clinical practice inspections in Chapter IV of Eudralex Volume 10.

4.4. General considerations regarding the schedule for activities related to GCP inspections

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 data being of insufficient quality. The CMS should communicate the need for a GCP inspection to the RMS by ideally day 30 of the MRP.

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 within 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.

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.

4.5. 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.

Where applicable, the RI writes an SIO which is forwarded to the requesting party. The conclusion of the SIO 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 (EMA/165056/2016) reports in chapter IV of EudraLex Volume 10. The template of the inspection reports given in the "Procedure for reporting of GCP inspections requested by the CHMP" EMA/INS/GCP/588734/2012 may be used as guidance 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.

Inspection reports should be made public once the inspection process is completed. The inspection report made public should be redacted, by the responsible inspectorate, in line with the principles set out in accordance with exceptions under Article 81(4) of the Regulation (EC) No 536/2014 and submitted in the EU portal and database, as laid down in Article 78(6) of the same regulation.

4.6. Consultation with the EMA GCP Inspection Working Group

The EMA GCP IWG, in line with the GCP IWG mandate, should be consulted in case Member States, the European Commission, EMA, scientific committees or CMDh require expert support on GCP related matters, in particular inspections.

If a Member State, CMDh or CHMP considers that the verification of compliance with GCP reveals divergences between the Member States involved, they should consult the CMDh and GCP IWG. The European Commission may request a new GCP inspection, when considered appropriate.

4.7. Consultation with the CMDh

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 CMDh member of the RMS or CMS requesting the inspection. This CMDh member should communicate this outcome to the plenary CMDh meeting or via the CMDh mailbox.

If the outcome of the GCP inspection is negative the CMDh together with 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 MAA and in the case of the MRP whether there is a need for referral in accordance with article 31 of Directive 2001/83/EC if the product is already authorised in some Member States). Consequences for other marketing authorisations should be also assessed.

5. Records

The RI arranges for archiving of the IRs of the inspections where he/she took over lead function, the SIO, its appendices and relevant inspection related documents. The LIs archive their IRs and inspection related documents according to the national procedures. The IR for each site inspected should be submitted through the EU portal as described in article 78(6) of Regulation (EC) No 536/2014.

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 are published in the Eudralex Volume 10.

Appendix I: GCP inspection request form 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 or EU CT 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

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	