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Guidance for applicants/MAHs involved in GMP and GCP inspections coordinated by EMA

GMP inspections

These inspections are requested by the Committee for Medicinal Products for Human Use and/or the Committee for Medicinal Products for Veterinary Use in order to verify compliance with Good Manufacturing Practice of sites responsible for the manufacture of centrally authorised products.

The details of each of the inspections adopted by the Committee(s), including the contact details of the persons in the inspection services who will be involved can be found in the IRIS Industry portal. Please let us know immediately if any of the information given has changed or is incorrect and if there are any problems with the proposed timing. The inspectors will contact you to finalise the dates and detailed arrangements.

Inspection fees

In accordance with Council Regulation (EC) No. 297/95, as amended, inspection fees are payable in connection with this inspection and an invoice for this will be sent to you by the EMA. For more information, please consult the *Fees website*. In addition to the inspection fees you are required by the same regulation to meet the travel and accommodation costs of the inspector(s) (and, if present, the expert), for sites located outside the EU/EEA. These expenses are to be paid directly by the applicant/MAH to the inspectors' authorities and according to the policy/requirements of the inspectors' authorities which may vary amongst the Member States. The applicant/MAH is kindly requested to assist with any travel arrangements following discussion and agreement with the reporting inspector.

In the case of a small and medium-sized enterprise (SME), you may be eligible for a fee reduction. Further information is available on the EMA website https://www.ema.europa.eu/en/human-regulatory/overview/fees-payable-european-medicines-agency.

Please provide via the IRIS Industry portal a purchase order (PO) reference number within 10 working days of inspection announcement. If your company does not have any internal purchase order number, please put N/A in the IRIS Industry portal. Purchase order information will be quoted on the invoice issued for the inspection carried out. Please note that the EMA will not accept delays on payments based on missing purchase order (PO) reference number information.

If you need any further information about the procedure to be followed for the inspections, please do not hesitate to contact the EMA Inspection Coordinator through the case in IRIS.

Legal basis:

- Articles 8(2), 33(2), 19(3) and 44(3) of Regulation (EC) 726/2004

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- Article 111(1) of Directive 2001/83/EC
- Article 80(1) of Directive 2001/82/EC

GCP inspections

These inspections are requested by the Committee for Medicinal Products for Human Use (CHMP) in order to verify compliance with Good Clinical Practice for centrally authorised products, in accordance with Article 57 of Regulation (EC) No. 726/2004, Article 15 of Directive 2001/20/EC and Article 78 of Regulation (EU) No 536/2014.

The details of each of the inspections adopted by the Committee, including the names and addresses of the investigational facilities to be inspected and the inspection services that will be involved can be found in the IRIS Industry portal. Please let us know immediately if any of the information given has changed or is incorrect.

The inspection will need to take place as soon as possible. The inspectors will contact you shortly to finalise the dates and the detailed arrangements for the inspection.

Please ensure that the sites of inspection are notified and that they are inspection ready and have relevant documentation, facilities and personnel readily available for the inspection. In this respect you (the applicant/MAH) and each inspection selected site must provide the EMA and inspectors with a written statement via the IRIS Industry portal. This statement should include that the sites selected for inspection accept to be inspected and that they will make available all documents required, including medical records/source data at the investigator sites, for direct access by the EU/EEA inspectors. This written statement needs to be provided prior to the departure of the inspection team to the inspection. Without this written statement, the inspection may not proceed. Restricting or obstructing the inspectors' access to information (data, documents, systems and/or, facilities) may provide grounds for non-acceptance of the trial data.

Please also advise the site(s) that as of the day of the announcement, for ongoing trials, IMP should no longer be returned from the site to the sponsor or sponsor's subcontracted CRO or destroyed.

As per Directive 2005/28/EC Articles 16 & 17 and Regulation (EU) No 536/2014 Articles 57 and 58, the trial master file (TMF) is the basis for the inspection and should be complete and readily available.

You should ensure that you have identified all trial documentation and its location that comprises the TMF and determined how this documentation will be made readily available to the inspectors. Please remember that the TMF may consist of trial relevant documentation held in files of various departments (e.g. pharmacovigilance, data management, statistics, R&D etc.) and various electronic systems.

When the sponsor has subcontracted activities, perhaps the TMF management itself to a contract research organisation (CRO), the TMF and/or the files and documentation held by the sponsor as part of their oversight will need to be available for inspection.

All the documentation that comprises the TMF (i.e. the documentation that enables the inspectors to evaluate the trial conduct) must be made available for direct access by the inspectors, including any electronic documentation for example email correspondence. Any equipment and software etc. to access any electronic documentation will need to be made available during inspection by the organisation.

Inspection fees

In accordance with Council Regulation (EC) No. 297/95, as amended, inspection fees are payable in connection with this inspection and an invoice for this will be sent to you by the EMA. For more information, please consult the *Fees website*. In addition to the inspection fees you are required by the same regulation to meet the travel and accommodation costs of the inspector(s) (and, if present, the expert), for sites located outside the EU/EEA. These expenses are to be paid directly by the applicant/MAH to the inspectors' authorities and according to the policy/requirements of the inspectors' authorities which may vary amongst the Member States. The applicant/MAH is kindly requested to assist with any travel arrangements following discussion and agreement with the reporting inspector.

In the case of a micro, small and medium-sized enterprise (SME), you may be eligible for a fee reduction. Further information is available on the EMA website https://www.ema.europa.eu/en/human-regulatory/overview/fees-payable-european-medicines-agency.

Please provide the following documents and information via the IRIS Industry portal within 10 working days of the notification of the inspection(s) or otherwise as agreed with the Reporting Inspector:

1. **A written statement from you (the applicant/MAH) and each site that is selected for inspection (e.g. the principal investigator for a clinical site) containing the following statement which should be signed and attached as a scanned copy if wet ink signed:** "The site(s) accept to be inspected and to make available all documents required, including medical records/source data at the selected investigator site(s), for direct access by the inspectors".
2. Contact names for the inspection, full addresses, telephone and email addresses for sites to be inspected.
3. A written statement confirming whether the applicant/MAH of this marketing authorisation application is the sponsor of the trial in question. If the applicant/MAH is not the sponsor, the applicant should provide a letter from the sponsor authorising that the inspection report can be released to the applicant by EMA. If such a letter is not received, the report will only be released only to the sponsor.
4. A written statement confirming that the trial participants enrolled/screened in the trial signed an informed consent stating that EU/EEA regulatory authority(ies) will be granted direct access to the trial participants' original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the trial participant, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the trial participant or the trial participant's legally acceptable representative is authorizing such access.
5. A purchase order (PO) reference number. If your company does not have any internal purchase order number, please put N/A in the IRIS Industry portal. Purchase order information will be quoted on the invoice issued for the inspection carried out. Please note that the EMA will not accept delays on payments based on missing purchase order (PO) reference number information.

Please provide only to inspectors (the reporting inspector should be contacted to discuss these requirements prior to submitting any documents):

An electronic copy (CD-ROM, DVD, IRIS or memory stick) of the following documents for the inspection team. Please ensure that documents are separate files and with meaningful filenames. Please send the information to each of the inspector(s) listed below **by a date agreed with the reporting inspector. Please liaise on this topic directly with the reporting inspector as soon as possible.** Documents containing text should be searchable files. Scanned copies are not acceptable for

documents that already exist in electronic format. For documents maintained in paper, e.g. the delegation log or trial participant screening/enrolment log, scanned copies are acceptable.

1. Complete clinical study report ([CSR], interim and/or final) with tables and all appendices. These appendices are expected to include all documents listed subsequently (based on ICH Guideline E3 - Structure and Content of Clinical Study Reports as Adopted by CPMP, December 1995, issued as CPMP/ICH/137/95) (please ensure also for these documents that they are separate files with meaningful filenames).
2. The protocol and all amendments.
3. A sample blank/template case report form (CRF).
4. A sample of any trial participant diary or other data collection tool ancillary to the CRF.
5. Trial participant information sheets and informed consent forms (ICFs) for the main study and all other ICFs used where applicable (e.g. sub-study, optional analyses, etc.):
    a. English master;
    b. If the ICF was country-specific (and not site-specific), national version used in the inspected country(ies) in local language(s), and full translation into English;
    c. If the ICF was site-specific, local version used at the inspected site(s) in local language(s), and full translation into English;
    d. For paediatric trials, all assent forms for all age ranges (master and national/local versions used) in addition to the parental/guardian ICF, with same requirements as above;
    e. If any of the above ICF was updated during the trial, all amended versions in track-changes mode, with relevant English translations.
6. The investigator's brochure and all updates.
7. The list of all participating clinical investigators with trial participant numbers (enrolled and/or randomized (if applicable)).
8. The individual trial participant data listings for the trial participants. These may be restricted to the selected investigator site(s), but confirmation should be sought from the reporting inspector prior to sending the documentation (including discontinued trial participants, protocol deviations, trial participants excluded from the efficacy analysis, demographic data, compliance and/or drug concentration data (if available), individual efficacy response data, adverse event listings, listing of individual laboratory measurements, etc.).
9. Listing of trial participants receiving test drug(s)/investigational medicinal product(s) from specific batches, when more than one batch was used.
10. The statistical analysis plan (documentation of statistical methods) and all updates.
11. The master randomisation list.
12. Audit certificates (if available).
13. Documentation of inter-laboratory standardisation methods and quality assurance procedures if used.
14. A list of publications based on the study.

15. Important publications referenced in the CSR.
16. Completed case report forms that allow easy navigation and hyperlinked with audit trail records.

Please also provide the following documents:

17. List of all third parties contracted such as CROs/vendors (names and addresses, contact person), contracted persons/freelancers/consultants and their role in the trial.
18. List of standard operation procedures (SOPs)/written procedures applicable to the conduct of the trial with version number and effective date for the complete time period of trial conduct.
19. The SOPs/written procedures covering the monitoring of the clinical trial and the monitoring plan (for onsite, centralised and remote monitoring as applicable). These SOPs/written procedures should include all versions in place for the complete time period of trial conduct.
20. An overview of all central monitoring activities and/or reports/documented results/outcomes of those.
21. Organisational chart/list of personnel involved in the trial (sponsor/CRO) and their role.
22. Communication plan.
23. Data-flow diagram that specifies flow of data in the trial(s) to be inspected from data generation to reporting, including depiction of electronic system interfaces and corresponding quality control steps.
24. The procedures for developments/maintenance and the table of contents or equivalent for the trial master file (TMF) (sponsor and investigator). State whether the TMF is paper-based or electronic, its location and how it will be made accessible by the inspectors.
25. List of all computerised systems used during/in/for the trial inspected (e.g. description, system owner, validation status, etc.).
26. Details of audit trails available for the electronic systems used in the trial. Please liaise with the inspector regarding the requested format of these (or specific extracts).

In relation to a sponsor/CRO site to be inspected, the following documents including all updates (as applicable depending on the site inspected and, for a CRO, the activities contracted to this CRO):

27. Data management plan.
28. Data validation plan.
29. A summary of activities undertaken, and decisions taken regarding proportionate approaches including mitigation activities in relation to the identified risks of the trial (e.g. in a risk assessment and mitigation plan).
30. The SOPs covering such approaches and a list/overview of all staff involved in identification and management of risks and their respective role in this process.
31. Risk-based monitoring strategy plan.
32. Trial management plan and any other relevant plan related to the trial.
33. Documentation of data review meetings/blind review meetings.
34. Documentation of independent data monitoring committee meetings and charts.
35. Manuals, instructions provided to contracted CROs/vendors.

36. Safety/pharmacovigilance management plan.

If any of the above documents are not applicable, please indicate so in the response. Additional documents may be requested by the reporting inspector after receipt of the documentation, as deemed necessary by the inspection team.

Please note that if interim data has been submitted in support of the application, measures should be put in place ensuring that the unblinded data are made available to the inspectors but still remain blinded as appropriate for the trial staff, when providing documents at any stage of the inspection.

For further details please consult the GCP Q&A, published on the EMA website, which provides useful guidance for stakeholders in relation to GCP inspectors expectations regarding some key aspects in the conduct of clinical trials and the format of the documents listed above (including trial participant data listings):

https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/qa-good-clinical-practice-gcp.

Any responses to a LoQ or LoOI in relation to the inspection must be addressed by the applicant to the inspection team in addition to the Rapporteur/Co-rapporteur, CHMP, EMA Product Leader (PL) and EMA Inspection Coordinator.

If you need any further information about the procedure to be followed for the inspection, please do not hesitate to contact the EMA Inspection Coordinator through the case in IRIS and/or the Reporting Inspector.

Legal basis:

- Article 57 of Regulation (EC) No. 726/2004
- Article 15 of Directive 2001/20/EC
- Article 78 of Regulation (EU) No 536/2014