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Co-ordinating GMP inspections for centrally authorised products

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Co-ordinating GMP inspections for centrally authorised products

1. Introduction

This guideline should be read in conjunction with the terms of the standard contract between the European Medicines Agency (EMA) and the Competent Authorities of the EU Member States.

2. Scope

For GMP inspections carried out by competent authorities of the Member States of the European Economic Area (EEA) at the request of the EMA.

3. Legal basis

In order to complete the assessment of applications for marketing authorisations under the centralised system the Committee for Medicinal Products for Human Use (CHMP) or the Committee for Medicinal Products for Veterinary Use (CVMP) may request that an inspection is carried out of the manufacturing site for a medicinal product in accordance with Articles 8 (2) of Regulation 726/2004 of the European Parliament and the Council and 94 (4) of Regulation 2019/6.

Repeated (routine re-inspections) may also be requested according to the provisions of Articles 19(3)of Regulation 726/2004 of the European Parliament and the Council and 94 (4) of Regulation 2019/6.

4. General procedure for GMP inspection

4.1 Inspections coordinated by the EMA are managed using the Corporate GXP application.

4.2 Inspection reports will be prepared by the inspectors of the supervisory authority of the Member State for all inspections requested by either the CHMP or CVMP under the obligations of Articles 18 of Regulation 726/2004 and Articles 123 (1) and 7 of Regulation 2019/6.

***Note**: Should a supervisory authority not be able to inspect in a third country, another competent authority may be requested to carry out the inspection following the Union procedure on delegation of responsibilities.*

4.3 The inspectors of the supervisory authority may be assisted in the preparation of the report by experts appointed by either the CHMP or CVMP to take part in the inspection.

4.4 The EMA requires the inspection report to be in English.

4.5 The content and format of the report should be that described in the Compilation of Union procedures.

4.6 The report should address any questions raised by the Rapporteur/Co-Rapporteur relating to the assessment of the manufacturing activities and/or control procedures or any other specific issues identified by the CHMP or the CVMP and/or the EMA (e.g. reported problems, quality defects) as relevant.

4.7 The inspection report should be finalised and sent to the EMA signed by all inspectors within the timelines identified in the relevant inspection request.

4.8 The EMA will check inspection reports received for adherence to this guideline and for their scientific content and overall quality. Reports, that in the opinion of the Agency are found to be deficient, incomplete or below the required scientific standard, will be returned to the authorities responsible for their preparation with a written explanation of the reasons for non-acceptance

and proposed deadline for revision, re-inspection or other remedial action. For pre-authorisation inspections this deadline will take account of the overall timetable adopted for completion of the assessment of the application.

5. Pre-submission notification by the applicant for a marketing authorisation

In their notification of intention to submit, applicants should mention the name (including contact point) and the address of the proposed manufacturers of the active substance(s) and finished product including the site(s) in the EEA responsible for batch release of the medicinal product. If necessary a flowchart should be provided to illustrate the role of all different sites involved. All sites listed in applications should be ready for inspection from the time of submission of the application and be in compliance with EU (or equivalent) Good Manufacturing Practice (GMP).

6. Designation of an inspection team and preparation for the inspection

The EMA validates submissions to the centralised system and determines whether or not an inspection of the manufacturing, control, batch release and importation site(s) concerned is needed to verify compliance with GMP before a marketing authorisation or a variation can be granted. A decision is made in collaboration with the (co)rapporteur whether or not to ask the relevant committee to adopt a request for an inspection. Such requests are adopted by the committee at day 90 or at the latest by day 120, and include any specific aspects of the application, that the (co)rapporteur raises in the day 70 assessment report(s), or analogous time point for variations.

In addition the EMA ensures that manufacturing sites listed in centralised marketing authorisations that are located in third countries are routinely re-inspected in accordance with the inspection frequencies laid down in the Compilation of Union Procedures in order to verify on-going GMP compliance unless an MRA or equivalent agreement is in force. Re-inspection of sites located in the EEA or in countries where an MRA or equivalent agreement is in force is left under the responsibility of the relevant National Competent Authorities.

The EMA will designate the National Competent Authorities that will form the inspection team. Normally the lead will be taken by the Supervisory Authority supported by another authority, in particular another Supervisory Authority if there is more than one. The EMA will consult the (co)rapporteurs, and EEA inspectorates as necessary and will, particularly in the case of re-inspections, attempt to distribute the workload among the Member States.

The National Competent Authorities participating in an adopted inspection request will nominate the inspectors who will carry out the inspection using the Corporate GXP application. The National Competent Authority shall not nominate inspectors that are not included in the list of EMA experts. EMA will check the status of the experts' nomination documentation before accepting the nominations.

When the Supervisory Authority is not able to inspect in a third country, a replacement competent authority will be found by EMA.

For routine re-inspections the EMA will propose an annual inspection plan in consultation with the Supervisory Authorities designed to distribute the workload evenly with support from other inspectorates as necessary.

7. Contacts with the applicant and the manufacturer(s) to be inspected

Once the Committee has requested an inspection, the EMA notifies the applicant/MAH that an inspection will take place, giving details of the inspection team and asks for the inspection fees to be paid.

Payments for inspections are made in accordance with the decision on a scale of fees adopted by the Management Board under Article 53 (3) of the Regulation. For inspections outside the EU, travel costs are paid directly to the inspectorates by the applicant/MAH in accordance with Article 5 (4) of Council Regulation (EEC) 297/95, as amended. The inspectors make the arrangements directly with the manufacturer and fix an inspection date and in the case of third country inspections should notify the local competent authority. In preparation of the inspection, the manufacturer(s) or the applicant/MAH may be asked to provide information about the site and operations to be inspected (this is normally provided in a "Site Master File"). The applicant may be requested to supply a copy of relevant parts of the dossier to the inspection team.

In the case of re-inspections the EMA will draw the attention to the inspection team of any specific issues that have been identified for inspection follow up for example arising from the last inspection, sampling and testing or quality defect investigations prior to the inspection.

8. Submission of the final report to the rapporteur and the EMA

One month after transmission of the inspection report to the manufacturer, the inspection team shall send their report to the EMA (by uploading and signing the report in the Corporate GXP application). The lead authority for the inspection is responsible for the issue of GMP certificates or statements of non-compliance in line with Union legislation and to update the EudraGMDP database accordingly.