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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 IRIS application.

4.2 Inspection reports will be prepared by the inspectors of the appointed authorities of the Member State for all inspections requested by either the CHMP or CVMP under the obligations of Articles 19(3) of Regulation 726/2004 and Articles 123 (1), (4)and 7 of Regulation 2019/6.

4.3 The inspectors of the appointed authorities 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 participating inspectors within the timelines identified in the relevant inspection request (i.e. Reporting deadline).

4.8 The EMA will check the 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. Triggers for inspections

Pre-approval inspections

The EMA validates submissions (new marketing authorization applications, line extensions and variations) 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 Supervisory Authority and the (co)Rapporteur whether or not to ask the relevant committee to adopt a request for a pre-approval inspection. Such inspections are identified at the stage of the validation of the marketing authorization or at receipt of the D70/D80 assessment reports, and need to be requested for adoption by the committee latest by day 90. The inspection will include, but not be limited to any specific aspects of the application, that the (co)rapporteur raises in the day 70/80 assessment report(s), or analogous time point for variations/line extensions.

Routine re-inspections

Once a site is registered in the dossier of a Centrally Authorised Product (CAP), via new marketing authorization application, line extension or variation, 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 and risk based approach 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 or MRA partner.

7. Designation of Leading and Supporting Authorities

All inspections requested by EMA should have a Leading Authority and a Supporting Authority. EMA will designate the Leading and Supporting authorities that will form the inspection team taking into account the following principles.

The Leading Authority is usually one of the Supervisory Authority for one/more product included in the inspection. The lead authority will be usually the SA that last inspected the site or, if not involved in previous inspection, the one with more products. The support will be the NCA that performed the last inspection (if not a SA) or one of the SA for the products manufactured/tested in the site.

Should none of the Supervisory Authorities for the products included in the inspection be able to conduct this within the timelines required, the EMA will request other competent authorities to carry out the inspection following the Union procedure on delegation of responsibilities. In the exceptional situation that no supporting authority is available, the inspection can be conducted by only one authority (the leading authority) who will have to assume the additional tasks to compensate for the

absence of a supporting authority.

In justified cases, if only one Supervisory Authority can be identified for the CAPs included in the inspection and there is national interest for that Supervisory Authority in view of need for inspections of the site for Nationally Authorised Products (NAPs), this Authority can act as Leading and Supporting Authority agreeing to take on the additional exceptional workload and related costs incurred by this inspection, provided also that no other National Competent Authority had informed EMA of their interest in acting as Supporting Authority.

In designating the Leading and Supporting authority, EMA will use the below criteria while ensuring that there is an adequate distribution the workload among the Member States and consistency and continuity for the inspected sites.

1. SA(s) of the products included in the inspection. When there is more than 1 SA for a specific site, EMA will consider the number of products (to be included in the respective inspection) that each authority is Supervisory Authority for. Consideration should be given to the NCA(s) performing the last inspection for consistency and continuity.
2. Inspector from Rapp and Co-Rapp NCA (for pre-approval inspections)
3. Call for volunteers to the GMDP IWG (as part of a specific request for inspection or in the annual re-inspection programme)

For pre-approval inspections, when identifying the Lead and Supporting Authorities EMA will consult the Supervisory Authority, the (co)Rapporteurs, as well as other EEA inspectorates (if other volunteers are necessary. Considering the short time frame to conduct and report pre-approval inspections for CAPs (usually between D80 and D121 of the MAA assessment procedure), the team composition must be determined as early as possible. Volunteers for a call for expression for pre-approval inspections should be provided within 14 days, unless otherwise specified.

For routine re-inspections the EMA will prepare an annual inspection plan in agreement with the EEA inspectorates from the GMDP IWG. The routine re-inspection programme is designed to identify Leading and Supporting authorities for all the registered 3rd country sites for CAPs while distributing the workload adequately within the EEA inspectorates. The composition of the team should be agreed at an early stage for better planning (twelve months before the end of the reporting deadline, but at least nine months in advance). Feedback on the proposed Lead and Supporting inspectorates as part of the EMA Re-inspection programme is expected during the consultation period in the margins of the IWG meetings, unless otherwise specified.

8. Preparation of inspections

Following the designation of the Leading and Supporting authorities for any inspection, together with the details of the inspections and reporting deadline will be requested for adoption by the CHMP and/or CVMP.

The National Competent Authorities participating in an adopted inspection request will nominate the inspectors who will carry out the inspection and inform the EMA by e-mail (i.e. by responding to the notification e-mail of the announcement of the inspection that is sent from IRIS) including the role (lead/supporting inspector) of each of the inspectors. The National Competent Authority shall ensure that inspectors are trained and are included in the list of EMA experts Database Tool before making the nominations. EMA will check the status of the experts' nomination documentation (i.e. Declaration of Interests) before accepting the nominations. Once this check is performed, the EMA will add the inspectors to the case in the IRIS system.

9. 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 National Competent Authorities that will conduct the inspection and indicates the inspection fees expected to be paid once the final inspection report is received by EMA.

Remuneration of inspections will be done by EMA in accordance with the financial Regulation (EU) 2024/568 and associated working arrangements on fees and charges payable to the European Medicines Agency applicable from 1 January 2025.

Travel expenses are paid directly to the inspectorates by the applicant/MAH in accordance with Article 1.4 of Annex IV of Regulation (EU) 2024/568.

EMA should be informed of the planned dates for inspection agreed between the appointed authorities (including the lead and supporting role of each) and of any changes in these dates, if applicable, as soon as they are scheduled. An inspection is considered scheduled once the specific dates have been confirmed by the inspecting NCAs and provided to the EMA. When more than 1 inspectorate are performing the inspection, the dates need to be agreed between the inspectors first as soon as possible, before EMA is informed.

The Leading and Supporting authorities will make the arrangements directly with the manufacturer and, once appropriate (closer to the inspection date), announce the inspection dates to the site. 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 third country inspections, the inspecting authorities should notify the local competent authority.

Prior to the inspection, 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 assessment of any regulatory submission (e.g. new marketing authorization application, line extension or variation), from the last inspection, sampling and testing or quality defect investigations by e-mail or via the IRIS system.

10. Submission of the final report to the EMA

Following the finalization of the inspection report, the inspecting authorities team shall send their report to the EMA (by uploading the signed report and the Appendix 1) in the case folder of the corresponding case via IRIS Network Portal)). EMA will validate the inspection report in accordance with the ''GMP inspection report- Union format'' as per Compilation of Union procedures on inspections and exchange of information, and raise any issue identified with the inspecting authorities, if needed. Once the inspection report validation has been completed by EMA, the payment process for the authorities will be initiated.

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.