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Inspections

Joint Audit Programme for EEA GMP inspectorates

JAP Programme

1. Scope

The scope of the Joint Audit Programme (JAP) is to verify the implementation of relevant provisions of European Union (EU) legislation into national laws, authorisation/licensing system for manufacturers and importers, Good Manufacturing Practices (GMP) compliance certification, administration of inspections, inspectorate, resources, complaints, rapid alerts including laboratory support, enforcement and internal quality assurance. The JAP covers all European Economic Area (EEA) GMP inspectorates in the field of medicinal products for human and veterinary use, including active substances.

The audit programme forms an essential part of the GMP inspectorate's quality system as referred to in the legislation (Directive 2003/94/EC) and adopted by GMP inspectorates as part of the Compilation of Union Procedures on Inspections and Exchange of Information. It ensures harmonised inspection standards and a harmonised approach to practical interpretation of GMP on the basis of European Union legislative requirements to support mutual recognition of inspection outcomes.

Additionally, and in order to satisfy requirements laid down in mutual recognition agreements (MRAs) and other legal agreements between the EU and some third countries, all member states have agreed to implement harmonisation of inspection practices and compliance procedures. This is particularly important in order to preserve confidence in the GMP compliance systems among MRA and other partners as agreed in the MRA and partners' maintenance programmes.

In order to meet these challenges and to preserve the confidence achieved both within the EU and at MRA level, the Heads of Medicines Agencies (HMA) group decided in October 2000 to set up a JAP with a view to evaluate their inspection systems, with the mission, wherever necessary, to implement corrective actions likely to guarantee the quality equivalency of these systems. Given the significant increase in the number of inspectorates responsible for medicinal products for human and veterinary use to be audited since the start of the JAP and the need to make best use of scarce resources, the principles of quality risk management have been included in the way it plans and conducts its audits and in the writing of reports. The JAP will also share inspection best practices with other EEA inspectorates, where possible and agreed with the auditee, in order to improve the effectiveness of the inspectorate network.

The HMA group has signed a letter of agreement with Pharmaceutical Inspection Co-operation Scheme (PIC/S), which entered into force on 15 August 2016, by which HMA and PIC/S agree to co-operate in

exchanging information in the context of the EEA JAP of GMP Inspectorates and the PIC/S Joint Reassessment Programme (JRP) of Participating Authorities.

2. Responsibilities

2.1. Compliance Group

The JAP is managed by the Compliance Group of the GMDP Inspectors Working Group (GMDP IWG) on behalf of the HMA group. Its role is to oversee the audit programme, prepare a rolling 5 year plan, assist in planning and co-ordinating the on-site visits and desk based assessments, review the outcome, adopt the audit report, coordinate follow-up of any corrective and preventive actions (CAPA), discuss and resolve where possible any major problem or present to the GMDP IWG any issue which cannot be resolved, update JAP documentation, prepare reports to HMA to be adopted by the GMDP IWG, define training courses for JAP auditors and exchange information with other regulatory bodies involved in audits concerning GMP inspectorates. The JAP related responsibilities of the Compliance Group are included in its mandate (EMA/364466/2014).

2.2. GMDP Inspectors Working Group

The main tasks of the GMDP IWG with respect to the JAP are:

- endorse the rolling 5-year audit plans;
- provide audit reports to the HMA group when deemed necessary;
- adoption of the Compliance Group mandate;
- nomination of the members of the Compliance Group;
- nomination of auditors and adoption of the audit notification;
- adoption/implementation of the documentation prepared by the Compliance Group;
- discussion/resolution of possible major problems, if escalated by the Compliance Group.

2.3. European Medicines Agency

The European Medicines Agency (EMA) provides coordinating support for the programme and it will:

- provide secretariat and technical, scientific, legal, regulatory and administrative support for the Compliance Group;
- prepare and coordinate the work of the Compliance Group;
- maintain the JAP documents including training materials;
- maintain and update the list of auditors and audit training records;
- maintain and update the list of audits carried out in the EEA;
- keep inventory of audit reports, CAPAs and follow-up measures;
- send out audit notifications;
- transmit recommendations of the Compliance Group to the GMDP IWG or other relevant body;
- draft reports to the HMA.

2.4. Heads of Medicines Agencies

The HMA group evaluates the programme on the basis of reports provided. The HMA will support the EEA JAP by providing the necessary resources. The HMA group could be asked to evaluate and to decide how to further proceed in case of uncorrected serious findings when escalated by the GMDP IWG.

3. General principles

3.1. Audit schedule

Audits should be performed every 5 years for every member state's GMP inspectorate and associated entities (e.g. OMCL, coordinating bodies) or outsourced activities after the initial full scope audit following the country's accession to the EU. With 44 GMP inspectorates in the EEA (excluding regional or federal ones), this results in 8 - 9 audits to be carried out per year. Audit prioritising and additional audits may be decided on the basis of risk which includes results from previous evaluations such as the number of findings and other signals such as significant changes identified in the annual MRA updates. Any additional audits should be based on specific requests if a Member State applies for it.

The Compliance Group sets up a rolling 5-year audit schedule annually, using the information held at the EMA and PIC/S, including a more detailed planning for the next 2 years. A risk-based approach is taken to plan the audits (e.g. time since last audit, number of findings during the previous audit, major changes to the organisational structure of the inspectorate or medicines agency, failure in the maintenance of standards of the GMP inspectorate). The audit schedule includes the EEA GMP inspectorates to be audited, auditors, date, Compliance Group sponsor, particular scope and rationale. For planning purposes, the Compliance Group liaises with PIC/S, according to the 2016 agreement, and MRA partners. The audit schedule is discussed and agreed by the GMDP IWG.

If they express interest, MRA partners may be invited to participate in particular JAP regular re-audits as observer or co-auditor. MRA partners may not participate as lead auditor, a position for which only EEA representatives are appointed. In case that an MRA partner is asking to participate as co-auditor, the inspectorate being audited and the GMDP IWG are informed via the audit notification.

Based on the audit schedule, the EMA officially announces the audits to the inspectorate. The EMA also requests Member States to designate auditors for specific audits.

3.2. Qualification and training of auditors

EEA auditors should be experienced inspectors or equally experienced staff (as co-auditors not observing GMP inspections) designated by the competent authorities or from EU Institutions. All auditors should be trained in this programme, either on-site or by remote access to JAP/JRP training materials, in particular in the scope of JAP audits, audit techniques and JAP procedures.

MRA partner representatives invited to participate in a JAP audit as co-auditor should have similar experience as requested from EEA auditors and be trained in the JAP programme, either on-site or by remote access to JAP/JRP training materials.

3.3. Audit procedure

A description of the necessary steps from initiating the audit, the desk-based phase of the audit, the full or limited scope on-site audit as required, to reporting on the audit and follow-up is given in a separate document titled JAP Procedure.

3.4. Coverage of the audit

The audit at the GMP inspectorate and any relating units or institutions should cover all or part (in case of a partial audit) of components of the audit checklist including the following aspects:

- quality system, including implementation of compilation of Union procedures on inspections and exchange of information;
- implementation of legislative requirements related to the GMP supervision system;
- authorisation/licensing system for manufacturers and importers;
- GMP guidance;
- GMP compliance certification;
- administration of inspections (e.g. frequencies, resources, procedures);
- qualifications and training of inspectors;
- inspections (planning, performance, reporting and follow-up system);
- complaints;
- Rapid Alerts system;
- obligations as EU Member State;
- internal audits;
- observed inspections (if carried out).

In addition, examples of best practice, where possible and agreed by the auditee, will be described to be included in an Annex to the audit report in order to share across the inspectorate network.

3.5. Audit report

It is the responsibility of the lead auditor to create the audit report including (if any) CAPAs and comments by the audited inspectorate, as well as a clear conclusion on fulfilment of each indicator from the audit checklist and the overall compliance with EU and JAP requirements. It is also the responsibility of the lead auditor to send the audit report to the audited inspectorate and the Compliance Group secretariat at EMA within the timeline indicated in the JAP Procedure document. The sponsor assigned by the Compliance Group reviews the audit report in liaison with the lead auditor, on behalf of the Compliance Group. The lead auditor takes into account the outcome of this review to update the audit report as appropriate. The Compliance Group should use information received for monitoring the progress after the audit and ensure that critical findings are brought to the attention of the GMDP IWG and the HMA group, if deemed necessary. The audit report and, if any, CAPAs (including a time frame for implementation) should be adopted by the Compliance Group. In case of unfulfilled indicators, the Compliance Group can escalate the issue, as appropriate.

On HMA's request, the EMA will draft a report on all audits performed, including the sharing of best practices if applicable. This report will be reviewed by the Compliance Group, agreed by the GMDP IWG and sent to the HMA group.

3.6. Follow-up measures

Where CAPAs identified in response to a JAP finding are not closed out by the time the audit report is adopted, follow-up of the remaining actions can be transferred to the Compliance Group supervision as

mentioned in the adopted audit report (as described in the JAP Procedure). Any inspectorate is entitled to this Compliance Group support until the resolution of all CAPAs. Once resolved in liaison with the audit team, the Compliance Group sponsor and the Compliance Group, the audit report is supplemented with a document describing the completion of the follow-up measures and the audit conclusion.

3.7. Translations

Usually the audit language is English, if not formally agreed otherwise. If translation for the auditors is needed, preferably an individual with technical expertise from the audited agency should provide the translation.

3.8. Guidance for MRA partners participating as co-auditor in JAP audits

MRA partners may participate in a JAP audit as co-auditor or observer but cannot act as lead auditor.

The lead auditor will communicate the following rules to the proposed MRA partner representative participating as co-auditor:

1. All MRA partner representatives will be expected to sign a confidentiality agreement in accordance with the relevant JAP procedure.
2. MRA partner representatives will be expected to complete an EMA declaration of interests (DoI) and curriculum vitae.
3. There should be no more MRA partner representatives than EEA JAP auditors.
4. In case any audit objective should be covered by the MRA partner representative alone in the framework of the MRA, or if any (potential) observation or opportunity for improvement would be raised by the MRA partner representative in the framework of the MRA, this should be preliminarily discussed with the lead auditor to confirm if EU legislation, rules, procedures or guidelines were effectively considered and impacted. In case of disagreement between the lead auditor and the MRA partner representative, this should be described clearly in the final audit report and the final evaluation of the subject matter of the disagreement can be referred to the Compliance Group.
5. All audit team members, including the MRA partner representative, should state any concerns during the audit to reach audit team consensus on the results, findings and conclusions. Decisions taken on-site by the audit team should not be challenged by members of the audit team afterwards.
6. JAP procedures lay down rules for the language in which the entire audit or different phases of the audits will be conducted and is designed for the efficient conduct of the audit. If translators are required by the MRA partner representative, this should be clarified well in advance of the audit and arrangements agreed with the lead auditor and auditee, and if applicable the inspected company.
7. MRA partner representatives are responsible for their own travel and accommodation costs, as well as any translation costs.

3.9. Guidance for observers of JAP audits:

The lead auditor will communicate the following rules to the proposed observers:

1. All observers (i.e. not limited to those observing GMP inspections) will be expected to sign a confidentiality agreement in accordance with the relevant JAP procedure.

2. Observers should not interfere with the conduct of the audit. They should not ask questions of the auditee during the audit itself. Questions may be asked of the JAP auditor(s) but the observer and auditor(s) should agree how and when this can occur before the audit starts.
3. Observers may not ask for copies of documents being assessed by the auditors before or during the audit. The final audit reports and observed inspection reports will only be shared with the agreement of the auditee. The preliminary audit report and observed inspection report(s) of the audit team and the GMP inspection report(s) of the auditee will not be shared under the terms of JAP.
4. The number of observers should be limited in order to avoid disrupting the conduct of the audit. As a general guide there should be no more observers than JAP auditors and the maximum number of observers should be linked to the expected number of audit teams. The JAP Procedure for observing inspections limits the number of auditors participating in the observed inspection to no more than 2 therefore it is reasonable to limit the number of observers to 1 per observed inspection.
5. JAP procedures lay down rules for the language in which the entire audit or different phases of the audits will be conducted and is designed for the efficient conduct of the audit. If translators are required by the observers, this should be clarified well in advance of the observed audit and arrangements agreed with the lead auditor and auditee, and if applicable the inspected company.
6. Observers are responsible for their own travel and accommodation costs, as well as any translation costs.

4. Audit programme cooperation

In order to avoid duplication of work, the Compliance Group through EMA cooperates with PIC/S, the MRA partners, other third countries with which the EU has a legal agreement and can look for synergies in other evaluation programmes, e.g. from the World Health Organisation (WHO), acknowledging that the WHO audit system is not identical to the JAP. A formal agreement is in place so that results from the JAP are acknowledged by PIC/S for the assessment/reassessment scheme without further duplication of activities and vice-versa.

Results of the JAP must not be shared with non-EEA partners unless specifically requested by the concerned member state.

5. Supporting documents

The JAP for EEA GMP inspectorates is described in a number of supporting documents listed below:

- JAP Programme;
- JAP Procedure;
- JAP Audit plan template;
- JAP Audit notification template;
- JAP Audit checklist;
- JAP Audit report template;
- JAP Confidentiality agreement for audits template;
- JAP Procedure for observing inspections;

- JAP Observed inspection checklist;
- JAP Follow-up on CAPA implementation template.

In addition, the Compliance Group secretariat holds training documents, annual audit schedules, reports to the HMA and the individual audit reports, their annexes and documents regarding follow-up measures.