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# Procedure for compliance management

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# Procedure for compliance management

## 1. Principle

In light of Article 111 of Directive 2001/83/EC, and Article 63(4) of Regulation 536/2004 and Article 123 of Regulation 2019/6, the compliance with the GMP and GDP principles should be verified by the means of inspections. If the outcome of the inspection shows that the inspected entity complies with principles of GMP and GDP, a compliance certificate shall be issued (Article 111(5) of Directive 2001/83/EC and article 94 (1) of Regulation 2019/6). In case of non-compliance of a site with principles of GMP or/and GDP, a statement of non-compliance shall be introduced to the EudraGDP base (Article 111(7) of Directive 2001/83/EC and article 94 (2) of Regulation 2019/6).

To ensure a continuous supply of quality medicines for human and veterinary use, it is in the interest of patients, animals, industry and regulators to take proactive action to address deficiencies in compliance with Good Manufacturing and Distribution practices as published by the European Commission in Eudralex Volume 4.

It is understood that a manufacturer or distributor can be considered to be in general compliance even if deficiencies requiring an improvement were identified, which the national competent authority is satisfied can be resolved in order to protect public or animal health. Action following the discovery of any of those issues should be commensurate with the level of risk posed.

The primary intention of early intervention (in the context of this procedure, 'administrative action') is to enable the company to ensure satisfactory compliance before regulatory action becomes necessary. However, in cases of continued non-compliance where this proactive approach is not yielding the required improvements, regulatory action may be considered.

Compliance management is appropriate in situations where the identified issues may not be effectively managed in the short term through a national competent authority's routine inspection process, especially in cases where it is considered that regulatory action (such as issuing statements of non-compliance or suspension of manufacturing / wholesale distribution authorisations) may not be necessary at that time. It is implemented independently by the national competent authority, and operates within the boundaries of the risk based inspection (RBI) process, with a view to avoiding the necessity of regulatory action by:

Figure: 1. Communicating the escalating compliance concerns to manufacturing / distribution authorisation holders and/or marketing authorisation holders.

Figure: 2. Developing a case management strategy to direct the site towards a state of satisfactory compliance, or (in the event of continued non-compliance) to gather evidence in preparation for consideration of regulatory action.

Manufacturers and distributors who are supervised through the compliance management process must be considered by the national competent authority to generally meet the rules governing medicinal products in the European Union which ensure the protection of public and/or animal health. Serious non-compliance by definition requires regulatory action to protect public or animal health to be taken without delay, in accordance with the Compilation of Union Procedures referring to serious GMP and GDP non-compliance.

The compliance management process does not replace or amend the regulatory actions described within EU medicines legislation at Union level, the Compilation of Union Procedures, and the equivalent provisions at national level in each Member State. It is not necessary for consideration of regulatory action to be preceded by the compliance management process. However, continued GMP and/or GDP deficiencies during the compliance management process may subsequently lead to consideration of regulatory action.

## 2. Definitions

**'Administrative action'** is defined as:

Measures taken by the national competent authority which do not result in regulatory action.

**'Regulatory action'** is defined as:

Action (suspension, compulsory variation or revocation) taken against the holder of a manufacture/ import authorisation, wholesale distribution authorisation, active substance registration, or marketing authorisation; publication of a statement of GMP or GDP non-compliance; or disciplinary measures taken against a named person (e.g. Qualified Person or Responsible Person) as a result of serious GMP or GDP deficiencies.

**'Compliance management'** is defined as:

The use of inspection and non-inspection monitoring measures to proactively manage manufacturing, importation and wholesale authorisation holders and manufacturers of active substances demonstrating deficiencies in GMP/GDP compliance or other risk indicators, when it is considered that routine inspection may not to be effective in achieving compliance improvements within a satisfactory time period.

**'Serious' GMP / GDP non-compliance** is defined as:

Non-compliance with GMP / GDP that in the opinion of the reporting inspectorate is of such a nature that regulatory action should be considered to remove a potential risk to public or animal health in accordance with national legislation and Compilation of Union Procedures for serious non-compliance.

## 3. Scope

The administrative actions described in this SOP are applicable to all GMP and GDP inspections whether in the territory of the national competent authority or in third countries, including inspections requested by the manufacturer, importer, the European Commission, the European Medicines Agency (EMA) or the European Directorate for the Quality of Medicines and Healthcare (EDQM). The procedure defines the administrative actions taken by the national competent authority following inspection of regulated activity/premises where GMP/GDP deficiencies require intervention to escalation of compliance concerns to authorisation holders for immediate attention if regulatory action is to be avoided. These administrative action principles are flexible in their application, to prevent conflict with national legislation in each Member State, and to permit compliance management to be commensurate with the specific deficiencies identified.

References within this SOP relating to action against Marketing Authorisations or Manufacturing / Import Authorisations are equally applicable to IMP dossiers submitted as part of a CTA, and MIA (IMP) authorisation holders. Marketing authorisation holders and clinical trial sponsors should also be considered synonymous for the purposes of this SOP.

References within this SOP relating to 'national competent authority' should be considered synonymous with 'EU supervisory authority' where compliance management is implemented following an inspection in a third country.

## 4. Procedure

This procedure describes the principles of compliance management which are designed to integrate with the risk-based inspection procedures of each national competent authority.

General GMP / GDP deficiencies should be managed within the risk based inspection process in the first instance. Compliance management is appropriate in situations where increased frequency of inspections is considered not to be effective in achieving compliance improvements within a

satisfactory time period.

## 4.1 Identification of unsatisfactory compliance requiring compliance management

The compliance management process in response to chronic or significant GMP / GDP deficiencies is usually initiated by an Inspector's recommendation, and continues with an internal review procedure in order to decide whether to support the recommendation, or whether alternative action is more appropriate.

Thresholds for initiating compliance management should be determined by the national competent authority. Examples include:

Figure: 1. Evidence of poor compliance history, for example:

Figure: 2. Number of major deficiencies;

Figure: 3. Repeated major deficiencies issued in successive inspections;

Figure: 4. Non-compliance with previous commitments to critical or major deficiencies.

Figure: 5. Unsatisfactory response to an inspection, for example:

Figure: 6. Failure to provide a response to inspection deficiencies;

Figure: 7. Unacceptable proposals for corrective and/or preventive action for major deficiencies;

Figure: 8. Unacceptable timescale for interim corrective actions or final preventive actions.

Figure: 1. The site requires direction and encouragement in achieving compliance by raising awareness of GMP / GDP obligations at a senior level (e.g. in future projects where the inspector believes there is significant risk of failure due to inadequate resourcing or planning by the company).

Any recommendation for regulatory action against a manufacturing or marketing authorisation (or refusal to grant an authorisation), regulatory action against a person named on an authorisation (e.g. Qualified Person) or recommendations for issuing a statement of non-compliance against one or more site activities must be managed within the procedures for serious GMP/GDP non-compliance described within EU medicines legislation at Union level, the Compilation of Union Procedures, and the equivalent provisions at national level in each Member State.

## 4.2 Supervision of manufacturers / distributors under compliance management principles (administrative actions)

Compliance management will vary depending upon the specific compliance issues identified. Inspection and non-inspection monitoring measures, or administrative actions such as communication of the national competent authority’s concerns to the authorisation holder senior management and conditioned (restricted) approvals may be used alone or in combination.

The rationale for administrative action, together with the case management strategy (including criteria for further escalation for regulatory action) should be documented within the national competent authority’s inspection record. This must include objective compliance-indicating measures, in order to assess progress over time.

### 4.2.1 Risk based monitoring

Risk based monitoring measures with frequency and scope relevant to the national competent authority’s concerns may be utilised. These include inspection measures, written progress updates and reporting of metrics to provide indicators of either progress with remediation plans and improving compliance, or further deficiencies which require consideration of regulatory action.

#### 4.2.1.1 Inspection measures

Re-inspection frequency and scope should be applied in accordance with the existing risk based inspection process. Compliance management input to inspection planning should ensure:

Figure: 1. Particular attention to the issues which resulted in the escalation for compliance management and evidence of progress with remediation, particularly in situations where the agreed corrective action plan is anticipated to continue for an extended period of time;

Figure: 2. Continued awareness of the overall inspection coverage for the manufacturer / distributor, to ensure that focus on specific areas of concern does not result in omission of other site activity inspections.

It may be possible to make optimum use of inspectorate resources by adjusting the normal risk based inspection interval on the basis of non-inspection monitoring measures such as periodic written updates or submission of metrics.

#### 4.2.1.2 Written updates and reporting of metrics

The authorisation holder's progress with corrective actions may be monitored between on-site inspections via remote assessment, where defined and appropriate. Care should be taken to ensure that the frequency of update submissions is commensurate with compliance concerns, and do not impede the organisation's progress with implementing their remediation plan.

Examples of written updates include:

Figure: 1. Periodic submission of the agreed action plan, demonstrating compliance with the proposed actions and completion dates;

Figure: 2. Reports from authorisation holder investigations into the specific compliance failures identified, and corrective actions arising;

Figure: 3. Evidence of continued senior management support to the remediation plan (e.g. high level progress reports signed by senior management, confirmation of adequate financial and personnel resources);

Figure: 4. 'Exception reports' submitted by the authorisation holder to notify the national competent authority of non-compliance with previously agreed action plans (e.g. delays in completing action), or identification of additional deficiencies as a result of further investigation work.

Metrics reporting may also be used as evidence of effective remediation. The metrics should be carefully selected to be specific and compliance-indicating, taking into account NCA resources and the GMP/GDP concerns which resulted in compliance management measures. For example, metrics relating to 'on time' stability sample analysis may be used as an indicator of improved management and resourcing of a previously deficient on-going stability programme.

The national competent authority should request the reporting of negative compliance indicators as well as positive indicators, as this ensures transparency in communication, facilitates the continued review of risk-benefit decisions by the national competent authority, and also informs the planning of future re-inspections. Metrics should be selected with care to avoid a perception that the NCA is taking over the responsibility of the manufacturer/ distributor.

#### 4.2.1.3 Market surveillance measures

Increasing regulatory oversight may include market surveillance sampling and testing of the company's products where relevant to the identified areas of concern. The national competent authority may also request increased level of quality defect reporting as an additional surveillance measure during a period of compliance management.

Such measures can supplement and support inspection-related activities.

### 4.2.2 Administrative action: 'Cautionary letters' – outlining compliance concerns and future regulatory actions if improvements are not made

'Cautionary letters' may be written to the manufacturer / distributor or marketing authorisation holder to outline specific compliance concerns, relevant company history, and the potential consideration of regulatory action in the event of continued GMP and/or GDP deficiency. Where appropriate, specific measures or milestones for future compliance assessment should be described.

Cautionary letters may be formatted in accordance with existing regulatory authority procedures for communicating with manufacturers, distributors and marketing authorisation holders. Consideration should be given to public visibility of cautionary letters where legislation permits. Where required, confidentiality requirements should be adopted.

The national competent authority will assess responses to cautionary letter(s). The outcome of this assessment should be considered when making decisions on the case management strategy and should follow a defined process.

#### 4.2.2.1 'Cautionary letter' to the manufacturer / distributor

Letters may make specific reference to routine obligations already imposed upon authorisation holders (e.g. ensuring only certification of product which is in compliance with its MA), but should not inform the company of specific corrective or preventive actions to address deficiencies. Letters should be signed by a senior person of the NCA who is not involved with the site inspection, as this further emphasises the nature and severity of compliance concerns.

Letters sent to the inspected manufacturer or distributor may be addressed to the Qualified Person or Responsible Person. In situations where the national competent authority believes that site senior management is not receiving relevant information from the Qualified Person or Responsible Person, or that they are not providing adequate oversight and support to ensuring compliance, the letter may be addressed to the site senior management. In the case of a large organisation, the letter may be addressed to senior corporate management. A response to this letter should be requested by the national competent authority.

The messages communicated in the letter to the Qualified Person, Responsible Person, or senior / corporate management will vary depending on the specifics of each case. Points to consider include:

Figure: 1. Reminding the manufacturer / distributor of their obligation to ensure that products are manufactured / distributed in compliance with EU GMP / GDP;

Figure: 2. Reminding the manufacturer of its obligation to ensure that products are manufactured in compliance with the relevant marketing authorisation(s);

Figure: 3. A request for the manufacturer's / distributor's assessment of the causal factors leading to the observed poor compliance observed during inspection;

Figure: 1. A request for senior management proposals to ensure an appropriate and suitably resourced plan to ensure that the manufacturer / distributor will be in compliance with EU GMP/GDP at the next inspection;

Figure: 2. Reminding the manufacturer / distributor of potential future escalation of regulatory actions caused by a non-compliance with GMP/GDP, which may include action against their authorisation, and/or issuance of a statement of non-compliance;

Figure: 3. A request to provide specific metrics or periodic written updates (as outlined in section 4.2.1.2);

Figure: 4. Reminding the manufacturer / distributor that an increased inspection frequency is anticipated until acceptable compliance is demonstrated;

Figure: 5. A request that the manufacturer or distributor should also inform all contract givers,

including the MAH, of the compliance situation. The NCA should have visibility of these communications to ensure that they are accurate and complete.

#### 4.2.2.2 'Cautionary letter' to the marketing authorisation holder

In situations where the national competent authority believes that the MAH has insufficient visibility of the inspected site compliance issues, or where MAH actions may be required to facilitate improvement and/or reduce the risk of supply disruption, a cautionary letter may also be sent to the MAH.

Consideration should be given to confidentiality provisions between the NCA and the inspected site prior to sending a cautionary letter to the MAH. Notification of the MAH by the inspected site (see section 4.2.2.1) may facilitate subsequent direct communication between the NCA and MAH, following national regulations.

The messages communicated in the letter to the MAH will vary depending on the specifics of each case. Points to consider include:

Figure: 1. Reminding the MAH of their obligation to ensure that products are manufactured in compliance with EU GMP and the marketing authorisation;

Figure: 2. A request for the MAH's assessment of the causal factors leading to the observed poor compliance history, including their oversight of manufacturing and/or distribution activities;

Figure: 3. The MAHs assessment of the inspection findings and their future plan to ensure that the manufacturer / distributor will be in compliance with EU GMP/GDP in an appropriate period;

Figure: 4. Reminding the MAH of potential future escalation of regulatory actions caused by the inspected site's non-compliance with GMP/GDP, which may include consequential action against the marketing authorisation;

Figure: 5. Request for the MAH's contingency measures in the event of a future supply disruption caused by a non-compliance with GMP/GDP;

Figure: 6. Reminding the MAH that increased frequency of inspection of the manufacturer / distributor is anticipated until acceptable compliance is demonstrated.

To ensure visibility of impacted products, the manufacturer should be requested to provide a list of all EU marketing authorisation numbers and MAH contact details.

The inspecting authority may liaise with the authority responsible for issuing the marketing authorisation regarding the content of cautionary letters to MAHs, when appropriate. In the case of cautionary letters relating to EMA-requested inspections for centrally authorised products (CAPs), EMA should be consulted. For inspections of relevance to CAPs conducted in the territory of a national competent authority, the periodic update outlined in section 5 of this procedure may fulfil this requirement.

### 4.2.3 Administrative action: Conditioned approvals (compliance-related GMP / GDP certificate restrictions, where no statement of non-compliance is proposed)

In order to reduce compliance risk at a manufacturer or distributor pending completion of corrective actions, it may be desirable for the national competent authority to condition a GMP or GDP certificate to add further short term regulatory controls.

Conditions may relate to restrictions such as:

Figure: 1. **Capacity**, e.g. 'GMP certificate cannot be used to support new marketing authorisation applications or variations';

Figure: 2. **Facilities or equipment usage**, e.g. 'EU approval is limited to production rooms x, y and z, pending improvement in cross contamination controls';

Figure: 3. **Reduced period of certificate validity**, e.g. 'GMP certificate is valid for 1 year from the date of inspection. After this time, continued validity should be confirmed with the issuing authority';

Figure: 4. **Change management**, e.g. 'In view of the potential for ineffective change management, existing post-approval change management plans may not be implemented from the date of issuing this certificate. Applications involving this site for new post-approval change management protocols should not be approved'.

Restrictions placed on a GMP or GDP certificate as a result of compliance management should be relevant to the specific compliance concerns, and periodically reviewed to confirm their continued suitability.

Communication of compliance restrictions with relevance to marketing authorisation dossier assessment should be visible to pharmaceutical assessors across the Union via the GMP certificate. Where confidentiality requirements prevent publication of these restrictions, they should be mentioned on the GMP certificate as a restriction comment visible to registered EudraGMDP users. In situations where a cautionary letter has been issued to the manufacturer or distributor, this should be mentioned on the GMP certificate as a restriction comment visible to registered EudraGMDP users.

In order to ensure transparency of increased regulatory scrutiny, the following statement should be included on the certificate in public view:

Figure: 1. 'GMP certificate issued with administrative action(s) described within the procedure for compliance management in the Compilation of Union Procedures'.

## 5. Communication of compliance management measures with relevance to other national competent authority's risk based inspection programmes

While compliance management is implemented by individual national competent authorities, it is beneficial for national inspectorates to have visibility of organisations under compliance management in one or more Member States.

Compliance management may be of relevance to more than one site in a multinational organisation. This may therefore impact the risk based inspection programmes of different EU national competent authorities, EMA and EDQM. To provide visibility to other national competent authorities, the planning module of EudraGMDP should be updated accordingly if the re-inspection of the site is changed as a result of compliance management activity.

Each national competent authority should make available information on sites under compliance management (organisation name and address) to other national competent authorities by providing searchable information in EudraGMDP for registered users. Inspectorates with an interest in one or more organisations identified should revert to the relevant national competent authority for further information under the existing EU exchange of information arrangements.

It should be remembered that a manufacturer or distributor under compliance management will, by definition, be considered by the national competent authority to remain acceptable for continued supply to the EU market, and will be in possession of a current GMP or GDP certificate. Member states should therefore consider information on compliance management sites as an intelligence input to risk based inspection planning, not as sites considered to be non-compliant and requiring immediate regulatory or market actions.

## 6. Closure of compliance management cases

Following a period of compliance management, a manufacturer or distributor may be found to have returned to a state of acceptable compliance, or may have failed to implement the required

improvements to a level where regulatory action should be considered.

Closure of compliance management cases should be indicated by updating EudraGMDP accordingly. In addition, the national competent authorities that requested information in accordance with section 5 should be informed whether sites have returned to routine inspection because of improvements or whether regulatory action is being taken.

Manufacturers and distributors who on subsequent inspection are found to demonstrate serious non-compliance with GMP or GDP will also be notified to national competent authorities via rapid alert following publication of a statement of non-compliance, in accordance with the Compilation of Union Procedures referring to serious GMP and GDP non-compliance.

## 6.1 Manufacturer / distributor has returned to acceptable state of compliance

Following a period of increased monitoring (see section 4.2.1), if a manufacturer has achieved the required level of compliance, the compliance management case may be closed. Routine supervision of the site will return to the inspectorate's routine inspection programme. It is conceivable that the site will retain a high risk rating within the RBI system until consistent compliance with EU GMP/GDP has been confirmed.

The return to the routine surveillance process should be notified to the manufacturer / distributor by the national competent authority.

## 6.2 Manufacturer / distributor has not achieved acceptable state of compliance

If the manufacturer / distributor fails to demonstrate the required improvements, or if compliance continues to deteriorate, the national competent authority should escalate the case for consideration of regulatory action. Evidence gathered during the period of increased monitoring (see section 4.2.1) may be used to support the proposal.

Recommendations for regulatory action should generally be supported by findings from a recent (typically less than 3 months previous) site inspection. This is to ensure that (i) indicators of declining compliance from desk-based review can be verified, and (ii) opportunities for legal challenge of subsequent regulatory action are minimised.

The escalation for consideration of regulatory action should be notified to the manufacturer / distributor by the national competent authority.