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Procedure for dealing with serious GMP non-compliance information originating from third country authorities or international organisations

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1. Summary

1.1 A consolidated procedure for dealing with all circumstances of serious GMP non-compliance information originating from third country authorities and international organisations is necessary to ensure a coordinated approach to potential risks to public/animal health. Information may refer to API, finished product or IMP manufacturers and/or QC labs located either in the EU/EEA or in a third country.

1.2 This document supplements the procedure in the Compilation of Union Procedures (CoUP) for dealing with serious GMP non-compliance, with regard to the receipt, dissemination and initial assessment of serious GMP non-compliance notifications which originate from third country (non-EU, non-MRA) authorities or international organisations (e.g. WHO).

1.3 The procedure requires the Competent Authorities in the EEA involved in the receipt and coordination of serious GMP non-compliance notifications to disseminate relevant information to all other authorities in the Union in a timely manner, to enable the scope and impact of the notification to be confirmed, and subsequent recommendations for action to be made.

1.4 Communication with authorities of those countries with which the Union has made appropriate arrangements on GMP (e.g. MRA) may also be necessary.

2. Definitions

2.1 For the purposes of this procedure, serious GMP non-compliance is non-compliance with GMP that in the opinion of the reporting authority is of such a nature that regulatory action is necessary to remove a potential risk to public/animal health. It should be noted that authorities in Third Countries issuing information may not share the same understanding.

3. Principles

3.1 Notification of serious GMP non-compliance from a third country authority or an international organisation should be assessed to determine the impact with respect to medicinal products supplied to the Union. It is possible that the detailed GMP non-compliances identified in the notification may have limited or no impact on EU products, e.g.:

Figure: 4. in cases where the issues relate to facilities or products which are not involved in EU supply, or;

Figure: 5. where the non-compliances do not relate to the principles and guidelines of GMP as defined in the relevant Directives and as interpreted in Guidelines on GMP published by the European Commission in Eudralex Volume 4, or;

Figure: 6. Where the impact of the identified non-compliances, as interpreted in Guidelines on GMP published in Eudralex Volume 4, do not pose a significant risk to the quality or safety of products for EU supply.

It is therefore important to determine the degree of Union impact as soon as possible following the initial notification.

3.2 Action following the notification of any non-compliance should be commensurate with the level of risk. Confirmation of serious non-compliance with the principles and guidelines of EU GMP by

definition requires regulatory action to be taken. Notification of GMP deficiencies which do not require regulatory action should be recorded in the relevant Supervisory Authority's model for risk based inspection planning, or compliance management, in accordance with CoUP.

3.3 The notification of serious GMP non-compliance may have implications not only for the Member State receiving the notification but also other, possibly all, Member States. Therefore a mechanism that ensures consistent, co-ordinated action throughout the Union is important, even though the final outcome may differ based on specific national factors.

4. Scope

4.1 This procedure relates to the receipt, dissemination and initial assessment of information relating to serious GMP non-compliance received from third country authorities. If, following assessment of the notification, the nature and severity of non-compliance is considered to pose a potential risk to public or animal health, coordinated regulatory action applicable to the situation should be considered in accordance with the detailed guidance provided in CoUP.

4.2 Procedures should require the adherence to timelines that ensure that serious non-compliance is dealt with in a timely manner.

Information shared by third country authorities may include situations where the GMP non-compliance does not reach the threshold of requiring regulatory action, and/or where measures equivalent to EU regulatory action are not proposed by the third country authority. In this case, the relevant national competent authority should review the notification. The necessary measures described under the risk-based inspection or compliance management procedures in the CoUP should be taken.

4.3 This procedure applies to all notifications of serious GMP non-compliance discovered by a third country authority or international organisations either in the territory of an EEA Supervisory Authority or in third countries. It applies to inspections of active substance manufacturers, manufacturers or importers of medicinal products, manufacturers or importers of investigational medicinal products as well as quality control laboratories.

4.4 Notifications of serious non-compliance with Good Practice in the case of human blood, blood components or tissues, when used as a starting material in medicinal products, may also follow this procedure.

4.5 All serious GMP non-compliance relating to active substance manufacturers and all types of manufacturers located in third countries must be communicated even if it is known that no other Member State has an interest at the time as it may be important for all Member States to have the information available in the future.

5. Procedure and Responsibilities

5.1 Receipt of third country Authority notification

5.1.1 A Member State who receives notification from a third country authority relating to serious GMP non-compliance at a manufacturer should ensure that sufficient information is obtained to permit an assessment of Union impact. Information to be collected includes:

- Contact details of single point of contact (SPoC) from the notifying authority
- Manufacturer name and address
- SPoC for manufacturer
- Product-related information
    - Human / Veterinary / IMP / API / export only
    - Products / dosage forms / buildings / lines affected

- Centralised / DC / MRP / national marketing authorisations / products not subject to a MA
- Non-compliance issues
  - EU GMP non-compliances
  - Third country GMP non-compliances

5.1.2 The coordinating authority may need to request further information from either the notifying third country authority, or the manufacturing site to which the notification refers, in order to ensure that the original information can be validated, and that sufficient information is obtained to permit an impact assessment in all Member States. Appendix 6 to the "Procedure for dealing with serious GMP non-compliance requiring co-ordinated measures to protect public or animal health" and associated guidance notes may be used to structure requests for additional information.

5.1.3 If an EU National Competent Authority receives a third country notification which refers to a manufacturer in its own territory, the notified National Competent Authority will take the necessary action. If the notification refers to a site in a different EU Member State, the notified National Competent Authority will forward the information to the National Competent Authority of the Member State in which the manufacturing site is located[1].

5.1.4 If the third country authority notification refers to a site in a third country, the coordinating authority is responsible for dissemination to all EU Member States and EMA, using the rapid alert single point of contact (SPoC) list[2]. If the information falls only within the scope of 'compliance management', this should be provided to the EU Supervisory Authority only.

5.1.5 Member States may receive further updates to the initial notification as additional information becomes available. These updates should also be circulated to ensure continuity of the information chain.

5.1.6 Each EU Competent Authority should have an internal national procedure to review this type of non-compliance information and determine whether there is any potential impact to products on their territory. Information relating to these products should be forwarded to the Member State who received the initial notification for collation, including information regarding product criticality (e.g. market share, and known availability of therapeutic alternatives).

5.1.7 The Member State who received the initial notification is responsible for arranging a teleconference with the concerned Member States to decide on the lead and on next steps. The selection of the coordinating Competent Authority will be based on a hierarchy of factors such as:

Product type	**Coordinator**
Centralised Product	Supervisory Authority will lead; EMA will co-ordinate actions.
DC / MRP	Supervisory Authority / Reference Member State
National Authorisation	Member State granting authorisation
IMP	Member State granting CTA
API	Coordinator responsible for the product type containing the affected API(s)

5.1.8 In cases where there are no EU-coordinated marketing authorisations but there are various National Authorisations affecting more than one Member State, the coordinating Competent Authority will be determined on the basis of product criticality or market volume. Consideration should also be given to inclusion of the Competent Authorities previously involved in GMP inspections of the site, as the Authority that has carried out previous inspections will be best

[1] Without prejudice to any confidentiality arrangements.

[2] Without prejudice to any confidentiality arrangements.

placed to assess the potential impact of the level of GMP non-compliance discovered.

5.1.9 Contact details for the coordinating Competent Authority SPoC should be sent to the notifying third country authority and the manufacturing site to which the notification refers.

5.1.10 If additional information becomes available during the process which indicates that a change in coordinating Competent Authority is appropriate (e.g. due to supplementary information on affected products), this should be agreed between the initial coordinator and the proposed new coordinator. Contact details of the new coordinator should be sent to the concerned Member States, and the contacts listed in section 5.1.8 above. Care should be taken to ensure that a change in coordinator is made only where absolutely necessary, and should be clearly communicated, in order to protect against confusion or delays in the assessment process.

5.1.11 The coordinating Competent Authority should continue to gather further information and clarification on the detailed inspection findings, impact on EU GMP and public/animal health. Coordination of issues with Marketing Authorisation Holders (MAH) may be required at this point, in order to determine potential impact on maintaining supplies. In cases where product is certified to the market by the holder of a Manufacturing and Import Authorisation who is not the MAH, information should also be obtained from the Qualified Person. Following collation of detailed GMP non-compliance and product related information, a risk assessment should be performed using Appendix 6 to the "Procedure for dealing with serious GMP non-compliance requiring co-ordinated measures to protect public or animal health" and associated guidance notes to determine the actions to be taken. Further guidance on the regulatory actions available for consideration is described in CoUP.

5.1.12 Consideration should be given with regards to whether an EU GMP inspection should be performed prior to taking any administrative action, or whether the significance of the issues notified require immediate action in the interest of public/animal health.

5.1.13 If the initial dissemination of information by the Member State which received the initial notification indicated that more than one Member State is affected by the notification of serious GMP non-compliance, a contact telephone number should be provided by the coordinating Competent Authority, together with a proposed time and date for a teleconference in which all affected Member States can join. This will assist in ratification of proposed regulatory action. EDQM should be invited to join the teleconference if a CEP is affected.

5.1.14 The coordinating Competent Authority will be responsible for communicating the agreed regulatory actions to the affected Member States using the template provided in Appendix 1.

5.1.15 The procedure post-communication should be followed as described in CoUP. An EU GMP inspection should be performed in order to verify the third country notification of non-compliances before consideration of issuing a statement of serious GMP non-compliance. In cases where this is not possible due to a perceived enhanced physical threat to inspectors (for political reasons, health reasons or others), the use of a 'distant assessment', as described in CoUP may be an appropriate alternative means to inform the decision regarding the issuance of a statement of serious GMP non-compliance.