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Procedure for dealing with serious GMP non-compliance requiring co-ordinated measures to protect public or animal health

Table of contents:

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Procedure for dealing with serious GMP non-compliance requiring co-ordinated measures to protect public or animal health

1. Principles

All GMP inspections carried out by the inspection services of any Member States are performed on behalf of the entire European Union. A GMP inspection report should make a clear conclusion as to whether a manufacturer or importer generally complies or not with the principles and guidelines of GMP as defined in Directive 93/2004/EC and/or 91/412/EEC and as interpreted in guidelines on GMP published by the European Commission in Eudralex Volume 4.

The discovery of serious GMP non-compliance may have implications not only for the member state carrying out the inspection but also other, possibly all, Member States. Authorities should endeavour to evaluate the consequences for public or animal health and agree in as far as practicable on common actions in advance of the issuance of the statement of non-compliance. Therefore a mechanism that ensures consistent, co-ordinated measures for protection of public and/or animal health are taken throughout the Union is required. Action following the discovery of any non-compliance should be commensurate with the level of risk posed by the non-compliance. Serious non-compliance by definition requires action to protect public or animal health to be taken without delay.

Where an inspection of an active substance manufacturer has been carried out at the request of the European Directorate for the Quality of Medicines and HealthCare (EDQM) in connection with the "Certification of Suitability to the monographs of the European Pharmacopoeia" inspectorates have a dual responsibility to follow this procedure for notifying national competent authorities of the serious GMP non-compliance and to follow the procedures established by EDQM to determine the consequences for the certification(s) in question. Inspectorates should ensure that a co-ordinated approach is followed.

Suspension or withdrawal of a Certificate of Suitability to the monographs of the European Pharmacopoeia (CEP) may be a recommended action following an inspection of an active substance manufacturer and so this procedure additionally addresses action to be taken in the event of notification by EDQM that a CEP has been voided or suspended for reasons other than serious GMP non-compliance as the actions and consequences are similar.

Although Member States may make a reasoned request to another Member State to receive an inspection report, the authority that carries out the inspection, with first-hand information is best placed to assess the potential impact of, and to manage the risk posed by, the level of GMP non-compliance discovered. This procedure requires the inspectorate discovering serious GMP non-compliance to recommend appropriate action following a supervisory risk assessment, involving other authorities that share supervisory responsibility in developing those recommendations, and to communicate the recommendations to all other authorities in the Union. Communication with authorities of those countries, with which the Union has made appropriate arrangements on GMP (e.g. mutual recognition agreement (MRA)) may also be necessary.

Provision is made in the procedure for a teleconference to give authorities receiving notification of serious GMP non-compliance an opportunity to seek clarifications and to confirm the appropriateness of the recommended actions before they are implemented.

National competent authorities (NCAs) must take into account the information on serious GMP non-compliance received and should provide information requested and follow the actions recommended, where the procedure requires it to do so, unless it can justify alternative action based on specific national considerations and where those alternative actions have no impact on other Member States.

The reporting inspectorate should enter the information on serious GMP non-compliance in EudraGMDP, as referred to in Article 111(6) of Directive 2001/83/EC (as amended) and Article 94 (2) of Regulation 2019/6 (as amended). In the case of a serious GMP non-compliance of an active substance manufacturer and where the inspection is in the context of the CEP, every effort should be made to align the entry of the final non-compliance statement into EudraGMDP with the final publication by EDQM of any supervisory action concerning affected CEPs.

Unnecessary communication of non-compliance should be avoided in order to make efficient use of the Union alert mechanisms.

With regard to supervisory actions, directly or consequential, against marketing authorisations, the Reference Member State (RMS) takes the initiative for mutual recognition/de-centralised products. Where more than one RMS is involved, a co-ordinated approach should be followed according to the "Best practice guidance on collaboration between Member States in relation to GMP non-compliance issues" of the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh). The Co-ordination Group for Mutual Recognition and Decentralised Procedures – Veterinary (CMDv) is involved in the case of veterinary medicinal products although no best practice guidance exists.

The European Medicines Agency takes the initiative and co-ordinates action for centrally authorised products (CAPs). Member States should ensure that their CMDh/CMDv or Committee for Medicinal Products for Human Use (CHMP)/Committee for Medicinal Products for Veterinary Use (CVMP) representative(s) as appropriate are involved in relevant discussion at national level during the evaluation phase and when implementing actions. Each national competent authority takes responsibility for marketing authorisations that exist purely at national level, but may wish to bring the discussion forward for collaborated evaluation at the level of CMDh or CMDv, according to the above mentioned CMDh procedure or CMDv.

GMP non-compliance may lead to a shortage of a medicinal product, if it is decided that it is necessary to prohibit importation and/or release of a batch or to withdraw batches from the market. It may be necessary to elevate the assessment to a union level in order to protect public or animal health.

The objective of the procedure should be to achieve a co-ordinated and harmonised (where possible) assessment and supervisory actions to ensure maximum efficiency and avoid full parallel reviews on a national level across the EEA.

It is understood that a manufacturer can be considered to be in general compliance even if there is degree of non-compliance, which the inspector is satisfied can be resolved without action to protect public or animal health being taken.

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 inspectorate is of such a nature that urgent interim supervisory measures may be necessary to remove a potential risk to public or animal health or where final measures may be needed to prohibit further supply of the medicinal product. Serious

GMP non-compliance may include deficiencies as a result of evidence of falsification gathered by inspectors during GMP inspection.

2.2 For the purposes of this procedure, urgent measures may include but are not limited to prohibition of manufacture or importation, supply or withdrawal of medicinal products, where the action may be limited to specific batches or suspension of an existing manufacturer or import authorisation.

2.3 For the purpose of this procedure final measures may include but are not limited to actions taken by an authority to revoke, or vary an existing marketing authorisation/manufacturer or import authorisation or refuse an application for marketing authorisation /manufacturer or import authorisation.

3. Scope

3.1 Most GMP inspections reveal a degree of non-compliance and even if failures to comply are cited as being "major", or occasionally, "critical", matters can usually reach a satisfactory conclusion, sometimes involving follow-up inspections, without supervisory action being taken. This procedure applies only when the level of non-compliance is such that the inspector concerned recommends that supervisory action is taken to remove a potential risk to public/animal health and that recommendation is ratified in accordance with internal national procedures. Procedures should require the adherence to timelines that ensure that serious non-compliance is dealt with in a timely manner.

4. Procedure for issuing a GMP non-compliance statement

This procedure should be followed, and if action to protect public or animal health is indicated this should be communicated to other competent authorities in accordance with this procedure, within a timeframe appropriate to the potential threat to public or animal health.

It may be necessary to issue the non-compliance statement without complete information if the risk to patient health is considered particularly severe.

4.1 Finalisation of inspection report and conclusion on GMP compliance

4.1.1 Finalise the summary of inspection findings: critical and major GMP deficiencies

Responsibility: inspection team

Following a GMP inspection leading to a conclusion of GMP non-compliance, the inspection team should have made their concerns clear to the inspected site. It may not be possible to finalise the inspection report in time to take the appropriate measures to protect public or animal health and therefore the inspection team should draft a summary of inspection findings describing the critical and major GMP deficiencies.

The inspection report may be prepared and finalised separately and should be available to competent authorities on request. The finalised report must conclude whether the inspected company complies with the principles and guidelines of GMP or not.

4.1.2 Review the summary of the critical and major findings

Responsibility: lead inspectorate authority

Each national competent authority should have an internal procedure to review inspection reports, (draft) non-compliance statements and supervisory risk assessments (refer to 4.2.3) prepared by its own inspectors which recommend administrative action in order to decide whether to support the inspectors recommended action or whether alternative action is more appropriate.

This internal procedure should take into account the need for co-operation and collaboration with other departments within the respective authority (e.g. market surveillance or pharmaceutical or clinical assessment) and with international partners where appropriate and with enforcement officers or national enforcement authority in the case of non-compliance due to falsification.

4.1.3 Finalise recommendations following assessment

Responsibility: lead inspectorate authority

Any recommendations made by the authority reporting the serious GMP non-compliance must take account of the interests of the Union as a whole, regardless as to any specific national considerations.

4.2 Pre-issuance of statement of non-compliance and supervisory risk assessment

Responsibility: lead inspectorate authority

If the inspection report concludes that the inspected company does not comply with GMP, then the lead inspectorate authority concerned should prepare a draft non-compliance statement and a supervisory risk assessment, discussing the impact of the inspection findings on medicinal products that are known to be on the market or in use in clinical trials or under evaluation at that time (and may be amended pending receipt of further information).

4.2.1 Gather information on the medicinal products manufactured at the site

Responsibility: lead inspectorate authority

In so far as is possible, the lead inspectorate authority that carried out the inspection revealing the non-compliance should establish the following as appropriate:

(a) The identity of Member States with products directly affected by the inspection findings.

(b) The marketing authorisations involved and where relevant, the RMS(s) and the competent authority(ies) responsible for the marketing authorisation(s).

(c) The identity of other supervisory authorities in the case of medicinal or investigational medicinal products or active substances imported into the Union.

(d) For investigational medicinal products the EudraCT trial reference numbers should be identified.

If serious GMP non-compliance is discovered at the manufacturer or importer of investigational medicinal products the impact on any completed or ongoing clinical trials will need to be taken into account in the recommendations of the lead inspectorate authority.

The lead inspectorate authority that carried out the inspection should involve the sponsor as well as the manufacturer or importer in order to identify all affected trials.

(e) In the case of inspections of active substance manufacturers, all the active substances manufactured at the site and/or any CEPs that may be affected.

4.2.2 Prepare a draft statement of non-compliance

Responsibility: lead inspectorate authority

The issuing authority should prepare a draft statement of non-compliance using the agreed Union format.

The draft statement of non-compliance should explain the nature of any proposed action, or where justified, action already taken.

4.2.3 Prepare the supervisory risk assessment

Responsibility: lead inspectorate authority

The inspecting authority's supervisory risk assessment should be appended to the draft statement of non-compliance.

The supervisory risk assessment should evaluate the critical and major GMP deficiencies and the overall risk to product quality and product supply and recommend what risk-mitigating action is appropriate. This could include i) a recall for products/batches released onto the market, ii) a prohibition of importation and/or supply and/or iii) administrative action with respect to the manufacturing or marketing authorisation or CEP, if appropriate.

The supervisory risk assessment should have the following structure:

(a) Introduction / background;

(b) Main inspection findings recorded which may lead to issuance of statement of non-compliance with GMP;

(c) Assessment of main inspection findings on concerned medicinal products, and whether these risks should be applied retrospectively from the date of the statement of non-compliance or earlier;

(d) NCA recommendations for interim urgent measures and final supervisory actions commensurate with identified risks. Any recommendations with respect to the marketing authorisation should be strongly motivated and commensurate with the level of risk;

(e) If an inspection of an active substance manufacturer has been carried out, the impact or otherwise on any other active substance manufactured at the same site and any CEP should be considered;

(f) Implications for product supply based on information available to the inspectorate.

A template for the preparation of the supervisory risk assessment is provided in Appendix 6.

4.2.4 Circulate draft statement of non-compliance & supervisory risk assessment

Responsibility: lead inspectorate authority

In principle unilateral action by one member state should be avoided, unless justified. In order to facilitate co-ordinated action at Union level, the draft statement of non-compliance should be circulated prior to the execution of any action.

The draft statement of non-compliance and supervisory risk assessment should be distributed to EEA Member States via the rapid alert distribution list. If an inspection of an active substance manufacturer has been carried out other than at the request of EDQM and serious non-compliance is found, EDQM should be included in the communication of the draft statement of non-compliance.

The lead inspectorate may request additional information from competent authorities and the timeframe indicated should take into account the level of risk and the amount of information to be gathered. National competent authorities should reply to the lead inspectorate by the timeframe indicated even if no impact is anticipated.

4.2.5 Receipt and evaluation of the (draft) statement of non-compliance and supervisory risk assessments

Responsibility: national competent authorities

On receipt of the draft statement of non-compliance, authorities should check whether nationally authorised products on their own territories are affected, and whether they are the RMS for any affected products, seeking assistance from the inspectorate carrying out the inspection, if different, as needed.

Member states and regulatory partner agencies who are in receipt of the draft statement of non-compliance and supervisory risk assessment must treat the documents and information contained therein as confidential. At this stage in the process it is unlikely that final regulatory or market place actions will have been agreed, and circulation of information outside the regulatory network risks a loss of coordinated action, with resultant risks to public and/or animal health. Communication with the manufacturing site should be coordinated via the lead inspectorate authority, and wherever possible communication with affected marketing authorisation holders or importers regarding compliance issues should be deferred until a consensus on coordinated action has been agreed across the Union.

Each national competent authority should have a procedure to review and, assess (draft) non-compliance statements and supervisory risk assessments transmitted through the rapid alert system. This procedure should take into account the need for co-operation and collaboration with other departments within the respective authority (e.g. product licencing, market surveillance or clinical or pharmaceutical assessment), and with the national licensing authority (where different) and with international partners where appropriate and with enforcement officers or national enforcement authority in the case of non-compliance due to falsification.

The procedure should ensure that information requested by an inspectorate can be obtained and returned within the timeframe indicated.

In cases where a non-compliance report will impact on a CEP, EDQM will evaluate the supervisory risk assessment and will decide on the action to be taken following their decision making procedure.

4.3 The teleconference

A rationale should be provided in the notification form if no teleconference is proposed.

Points to consider for authorities on when to hold a teleconference and practical arrangements in hosting the teleconference are appended to this procedure (Appendix 2).

4.3.1 Organising the teleconference

Responsibility: lead inspectorate authority

Where relevant, a contact telephone number should be given in the draft GMP non-compliance notification form together with a proposed time and date for a teleconference in which all affected Member States can join, and in which co-ordinated action can be ratified.

The EDQM should be invited to join the teleconference if the non-compliance relates to an active substance manufacturer named on a CEP.

4.3.2 Joining the teleconference

Responsibility: national competent authorities

If a member state is affected, or if a Member State is RMS for a product that is affected, they should join the teleconference if there is to be one. If no teleconference is proposed, receiving authorities should, where appropriate, take the actions on its own territory that correspond with the actions proposed or already executed by the authority reporting the non-compliance. If the proposed actions include variations to Marketing Authorisation(s) the RMS(s) should take the lead in implementing such actions.

The objective of the teleconference should be to co-ordinate and harmonise where possible the assessment and actions to ensure maximum efficiency and avoid full parallel reviews on a national level across the EEA.

4.3.3 Communicating the outcome of the teleconference

Responsibility: lead inspectorate authority

The outcome of the teleconference, if held, should be communicated in a follow up message to the network via rapid alert contact points to confirm that the recommended action in the initial notification was agreed or to communicate any other agreed Union action.

4.4 Urgent measures to protect public and animal health

On receipt of the draft non-compliance statement, receiving authorities should verify the implications for public and animal health and adapt national actions as necessary.

4.4.1 Evaluating the impact of the GMP non-compliance statement on the quality and safety of batches on the market or awaiting release

Responsibility: lead inspectorate authority

The lead inspectorate authority reporting the serious GMP non-compliance should recommend if urgent interim measures to safeguard public and/or animal health by removing batches from commercial circulation or in use in clinical trials and/or to prohibit further distribution and/or importation of concerned batches is necessary. The lead inspectorate authority should evaluate, where possible, the impact of the GMP non-compliance statement on the quality and safety of batches on the market or awaiting release. In cases where such evaluation is not possible due to insufficient information, the lead inspectorate should provide support to this evaluation process by supplying details regarding the deficiencies observed and the potential global impact of the products.

Recommendation on recall or prohibition of supply should be discussed with the relevant authorities at the teleconference. As far as practicable a harmonised Union action plan and

timetable should be achieved and agreed. It is recognised that in some cases different actions may be necessary in different Member States due to the criticality of the medicinal products concerned. Criticality of medicinal products should be assessed following agreed criteria (Appendix 3). Differences in approach should be recorded in the minutes of the teleconference.

In the event that supply shortages will be caused at a Union level, as a result of proposed measures to be taken due to non-compliance with GMP, consideration should be given to initiating the procedure described in "The European Union regulatory network incident management plan for medicines for human use" or the corresponding procedure for veterinary products. In the case of medicinal products for human use, further guidance on when it is necessary to elevate the discussion to Union level in order to agree on a harmonised risk management strategy in order to protect public health is available (Appendix 4).

4.4.2 Deciding to issue a rapid alert

Responsibility: lead inspectorate authority

If it is considered necessary to remove products or certain batches from the market, the lead inspectorate authority is responsible for issuing the rapid alert. If there is a differential approach to product recall in Member States, agreement should be reached on responsibility for transmission of the initial rapid alert.

Recalls and rapid alerts should be classified and transmitted in accordance with Union procedures.

4.4.3 Deciding to prohibit supply

Responsibility: supervisory authority / competent authority

It may be necessary to urgently prohibit importation and supply through an appropriate supervisory measure.

4.5 Publication of statement of non-compliance

4.5.1 Finalisation and entry into EudraGMDP

Responsibility: lead inspectorate authority

The lead inspectorate should then finalise the statement of non-compliance and/or restricted GMP certificate (see 4.5.3) and enter into EudraGMDP.

4.5.2 Impact on other EudraGMDP entries for the manufacturing site

Responsibility: lead inspectorate authority

Existing valid GMP certificates with conflicting information will be superseded and should therefore be withdrawn in accordance with the Union procedure for the issue and update of GMP certificates.

4.5.3 Entry of restricted GMP certificate into EudraGMDP

Responsibility: lead inspectorate authority

If, following discussion at the teleconference, a risk-based decision is agreed to allow further release and distribution of batches of critical product(s) from the site concerned, an

appropriately restricted GMP certificate may be issued as well as a statement of non-compliance.

In other cases, if the non-compliance is partial e.g. involving a limited category of dosage forms, a new GMP certificate might also be issued, but restricted as appropriate.

4.5.4 Notification of relevant authorities where the manufacturer is located

Responsibility: lead inspectorate authority

Where the GMP non-compliance is discovered at a third country manufacturing site the inspectorate concerned should notify the relevant authorities of the third country of the issuance of the statement of non-compliance. The inspectorate should seek co-operation from the concerned third country authority in overseeing correction at the manufacturing facility.

In the case of third country manufacturers of active substances, the concerned third country authority should be notified of the issuance of the statement of non-compliance using the template provided in Appendix 5. The third country authority should be asked to withdraw any previously issued written confirmations of API compliance, and to notify the supervisory EU authority when compliance equivalent to EU GMP is considered to have been restored by the manufacturer. As the statement of non-compliance takes precedence over a written confirmation, resumption of supply to the EU may take place only following a satisfactory re-inspection by an EU authority, or MRA partner agency (if recognition of inspections in third countries is covered by the MRA).

4.5.5 Notification of MRA partners

Responsibility: lead inspectorate authority

In the context of an MRA, partners are obliged to notify recipients of GMP certificates exchanged when those certificates are withdrawn due to GMP non-compliance. This is done automatically by EudraGMDP.

4.5.6 Notification of third countries

Responsibility: lead inspectorate authority

Third countries with which the Union has concluded an arrangement and which have been given access to EudraGMDP will be notified automatically of statements of non-compliance placed into the database.

In the case of a non-compliance statement issued following an inspection of a manufacturer of active pharmaceutical ingredients located in the EU, the lead inspectorate should notify the authority of any third country that is supplied by that manufacturer. Notification may consist of a statement that a non-compliance statement has been uploaded to EudraGMDP.

4.5.7 Post-publication modifications

Responsibility: lead inspectorate authority

Following the publication, the lead inspectorate authority may have to modify the non-compliance information entered in EudraGMDP for example, following receipt of new information. The modified statement of non-compliance should be distributed to the rapid alert distribution list drawing attention to those sections that have been altered.

4.6 Non-Urgent Measures to protect public and animal health

On receipt of the final non-compliance statement, receiving authorities should verify the implications for public and animal health and adapt national actions as necessary.

4.6.1 Evaluating and deciding the impact of the statement of non-compliance on marketing authorisations (applications)

Responsibility: EMA or RMSs (including consultation with CMSs and discussion at CMDh/CMDv if necessary)

The evaluation of the impact of the statement of non-compliance on marketing authorisations (applications) should take into account the appropriate legal framework for granting the marketing authorisation as well as the potential impact of the findings on any data submitted to the competent authority. Any decision to suspend a marketing authorisation has to be strongly motivated and the principle of proportionality taken into account.

In the case of evaluation of the impact on marketing authorisations (applications) subject to the de-centralised/mutual recognition procedures, the RMS should take the initiative in following the recommendations of the authority reporting the non-compliance.

In the case of actions proposed for marketing authorisations (applications) subject to the de-centralised or mutual recognition procedures, CMDh or CMDv may decide to discuss the coordination of actions at a meeting of the relevant group before implementation.

In the case of action against centralised marketing authorisations (applications), the European Medicines Agency will co-ordinate evaluation via the CHMP and/or CVMP.

Each national competent authority takes responsibility for marketing authorisations (applications) that exist purely at national level, but collaboration at EU level may be sought by tabling the issue for further discussion at CMDh/CMDv.

The appropriate competent authorities should decide whether a marketing authorisation should be suspended, revoked or varied and/or whether a marketing authorisation application should be refused as a result of the non-compliance with GMP.

Automatically suspending marketing authorisations associated with a non-compliant manufacturing site, where no alternative manufacturing site is authorised, may not always be the most appropriate approach since if the manufacturing activity is suspended, then this alone should serve to protect public/animal health. If the suspension or revocation of the manufacturing authorisation is partial, then not all marketing authorisations listing the site will be affected. It may be possible to protect public health through the removal of a noncompliant site through variation of the marketing authorisation.

Member States should inform EMA as appropriate following the procedure in Article 123 of Directive 2001/83/EC (as amended) for human medicinal products. For veterinary products in the absence of a specific legal basis in regulation 2019/6, the national competent authorities have agreed to follow the principles of the procedure set out in article 123 of Directive 2001/83/EC for human medicinal products.

4.6.2 Evaluating and deciding on the impact of the GMP non-compliance statement on clinical trials

Responsibility: national competent authorities

Where action may have an impact on clinical trials, national competent authorities should involve the Clinical Trial Facilitation Group (CTFG).

Each national competent authority authorising the trial in question should evaluate the impact of the GMP non-compliance statement on the quality and safety of the investigational medicinal product and in some cases the results of completed trials may need to be re-evaluated.

Each national competent authority authorising the trial in question should decide on the appropriate measure to be taken.

Where the agreed action is suspension or termination of a clinical trial each national competent authority having authorised the trial in question should make an appropriate entry into the EU clinical trial database.

4.6.3 Evaluating and deciding on the impact of the GMP non-compliance statement on CEPs

Responsibility: EDQM

If an inspection of an active substance manufacturer has been carried out at the request of EDQM and serious non-compliance is found, the EDQM is responsible for evaluating and deciding on the impact of the non-compliance statement on the CEP(s).

The lead inspectorate and EDQM should ensure that issuance of the final statement of non-compliance with GMP should be aligned with the issuance of the final decision of EDQM's ad-hoc committee on the validity of CEP(s).

4.6.4 Evaluating and deciding on the impact of the GMP non-compliance statement on manufacturing / import authorisation(s)

Responsibility: supervisory authority

Supervisory authorities should evaluate whether a manufacturing or import authorisation should be suspended (total or partial), varied or revoked as a result of the non-compliance with GMP. Similarly, an application for a manufacturing or import authorisation may be suspended or refused.

The Supervisory Authority should decide whether a manufacturing or import authorisation should be, suspended (total or partial), varied or revoked as a result of the non-compliance with GMP.

The supervisory authority should decide on the consequential entry required in the EudraGMDP database.

GMP non-compliance found at an active substance manufacturer may indicate that manufacturing authorisation holders using the active substance in question as a starting material have failed to fulfil their legal obligations and therefore action may be taken against the manufacturing or import authorisation or QPs connected with it.

4.6.5 Evaluating and deciding on the impact of the suspension or withdrawal of the CEP on the marketing authorisation (application)

Responsibility: RMSs (including consultation with CMSs and discussion at CMDh/CMDv if necessary) EMA / or NCA's

If a CEP is suspended or withdrawn the appropriate competent authorities should assess the reasons for the suspension or withdrawal and decide whether a marketing authorisation should

be suspended, revoked, or varied and/or whether a marketing authorisation application should be refused as a result of the consequent suspension or withdrawal of the CEP due to the non-compliance statement.

The appropriate competent authorities should consider requesting that alternative active substance manufacturer be added through a variation unless an alternative active substance manufacturer is already authorised, in which case the non-compliant active substance manufacturer should be removed through a variation.

5. Suspension or withdrawal of CEPs for non-GMP reasons

CEPs may be suspended or voided for reasons unrelated to inspections, for example failure to fulfil critical commitments.

5.1 Notification to the European medicines regulatory network

Responsibility: EDQM

In cases where a CEP has been voided for non-GMP reasons, EDQM notifies all national competent authorities using the agreed contact points. In its notification EDQM should clearly indicate the reasons for suspension or withdrawal.

5.1.1 Evaluating the impact of the suspension or withdrawal of the CEP on quality and safety of batches on the market

Responsibility: RMS (including consultation with CMSs and discussion at CMDh/CMDv if necessary) / EMA / NCA

Reasons for CEP withdrawal or suspension other than noncompliance with GMP may include but are not limited to for example, the inability to manufacture in accordance with the current monograph (i.e. when a revised monograph has been introduced), impact of local regulatory restrictions placed on the manufacturer (e.g. environmental) or temporary interruption of manufacturer at the request of the CEP holder based on commercial reasons.

In the event that a recall is necessary in response to CEP withdrawal or suspension for reasons other than noncompliance with GMP, responsibility for issuing the rapid alert is as follows:

Figure: 1. For affected products subject to the decentralised or mutual recognition procedures the Reference Member State,

Figure: 2. For centrally authorised products, the European Medicines Agency will co-ordinate in the same way as a quality defect.

Figure: 3. For products subject to national marketing authorisations only, a national recall may suffice.

5.1.2 Evaluating and deciding on the impact of the suspension or withdrawal of the CEP on the marketing authorisation (application)

Responsibility: RMS (including consultation with CMSs and discussion at CMDh/CMDv if necessary) / EMA / NCA

Following notification by EDQM, each competent authority should establish whether they have issued national marketing authorisations that depend on the CEP(s) in question, and, where relevant, whether it is a RMS.

The European Medicines Agency through the scientific committees, will assess any impact on centrally authorised products and co-ordinate any associated supervisory action.

The RMS should take the initiative in proposing an action on marketing authorisations subject to the mutual recognition or de-centralised procedures and consulting with the CMSs and the decision is taken nationally. The appropriate competent authorities should assess the reasons for the suspension or withdrawal and decide whether a marketing authorisation should be suspended, revoked, or varied and/or whether a marketing authorisation application should be refused as a result of the consequent suspension or withdrawal of the CEP.

The appropriate competent authorities should consider requesting that alternative active substance manufacturer be added through a variation unless an alternative active substance manufacturer is already authorised, in which case the active substance manufacturer named on the CEP in question should be removed through a variation.

Individual national competent authorities should take action against the marketing authorisation in the case of products authorised solely on a national basis.

6. Disagreements

6.1 Disagreeing with the outcome of the inspection

Responsibility: national competent authorities

Disagreement with the outcome of the inspection should be dealt with through procedures established in accordance with Art. 122 of Directive 2001/83/EC (as amended) for human products. In such cases Art. 122(3) of Directive 2001/83/EC obliges the Member State in question to notify the European Medicines Agency and the Commission. For veterinary products in the absence of a specific legal basis in regulation 2019/6, the national competent authorities have agreed to follow the principles of the same arbitration procedure set out in article 122 of Directive 2001/83/EC for human medicinal products.

6.2 Disagreeing with the outcome of the assessment of the impact of the non-compliance statement

Responsibility: national competent authorities

Exceptionally, where, following proper assessment, specific national factors alter the risk such that the agreed Union action in connection with a marketing authorisation, or a rapid alert is not considered, on balance, to be in the interest of public health in any particular Member State, that Member State may decide to take alternative action to that proposed by the Member State initiating this procedure so long as this does not affect any other Member State.

7. Appendices

Appendix 1: Flowchart

Appendix 2: Points to consider when a teleconference is convened by the lead inspectorate authority

Appendix 3: Criteria for classification of critical medicinal products, EMA/314762/2013

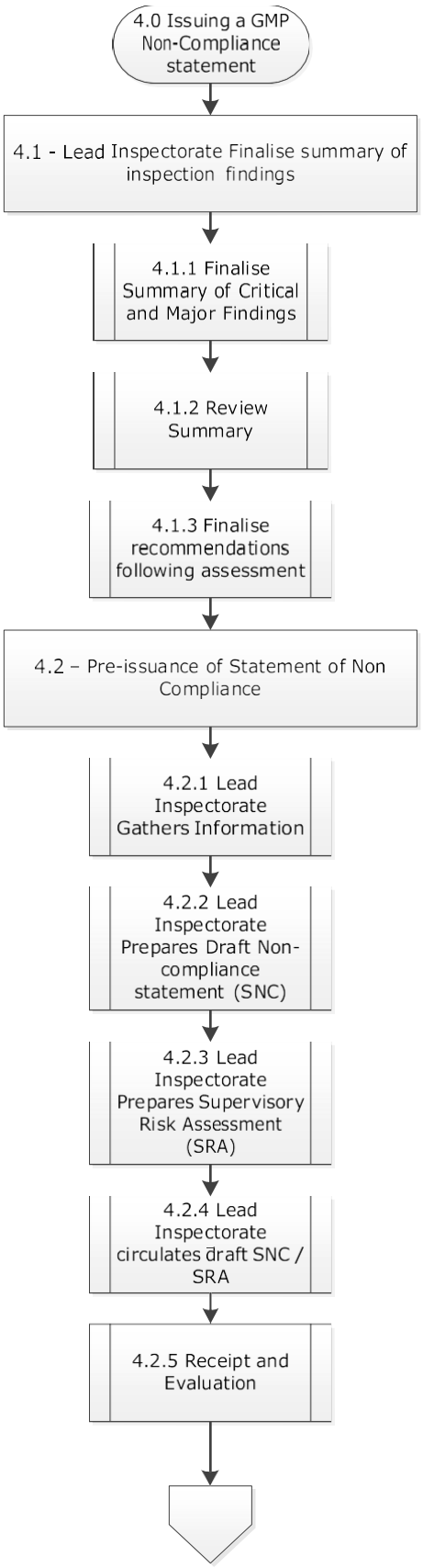
Appendix 4: Decision tree on escalation from national to European level, EMA/314722/2013

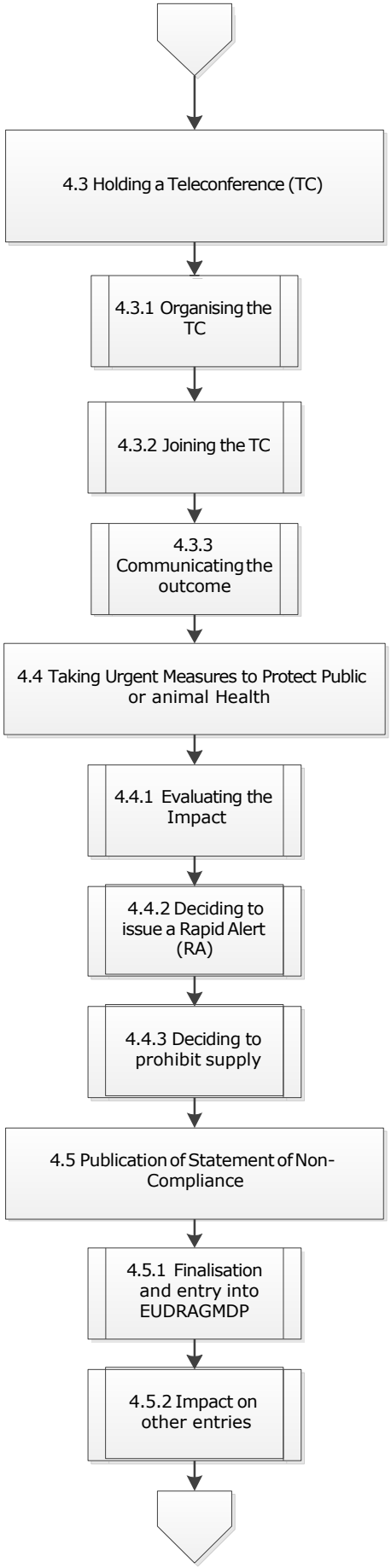
Appendix 5: Template to 3rd country authorities issuing written confirmations

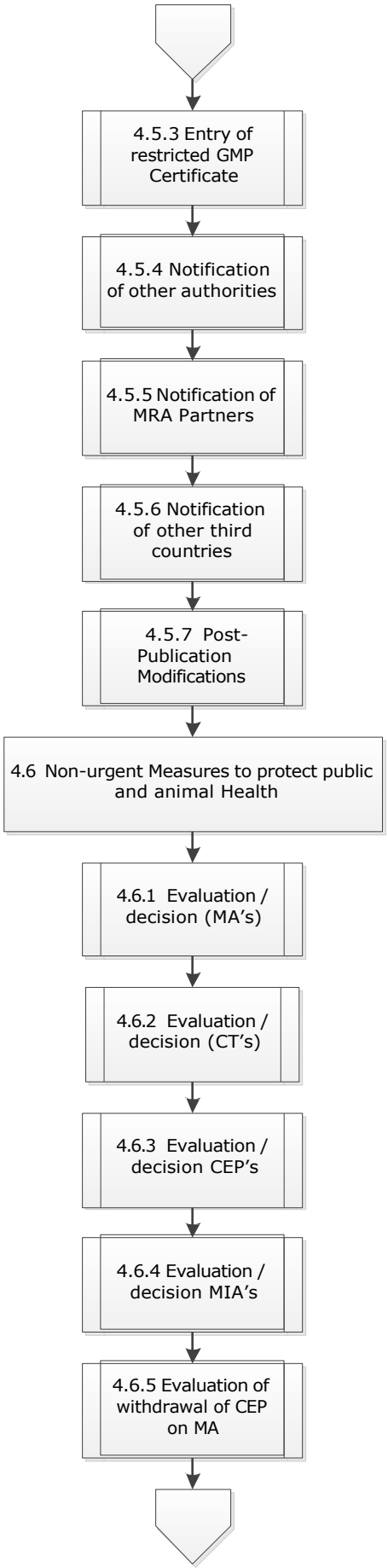
Appendix 6: Supervisory Risk Assessment

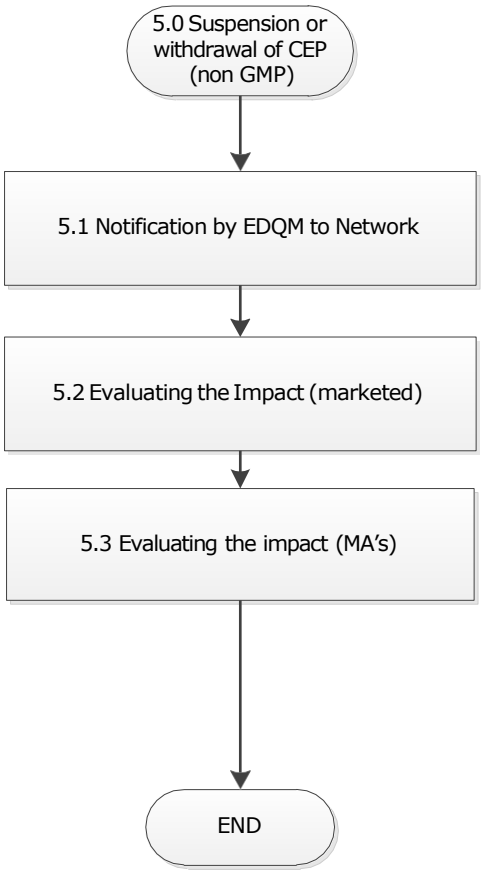
Appendix 1:

Annex 1




4.3 Holding a Teleconference (TC)
4.3.1 Organising the TC
4.3.2 Joining the TC
4.3.3 Communicating the outcome
4.4 Taking Urgent Measures to Protect Public or animal Health
4.4.1 Evaluating the Impact
4.4.2 Deciding to issue a Rapid Alert (RA)
4.4.3 Deciding to prohibit supply
4.5 Publication of Statement of Non-Compliance
4.5.1 Finalisation and entry into EUDRAGMDP
4.5.2 Impact on other entries


4.5.3 Entry of restricted GMP Certificate
4.5.4 Notification of other authorities
4.5.5 Notification of MRA Partners
4.5.6 Notification of other third countries
4.5.7 Post-Publication Modifications
4.6 Non-urgent Measures to protect public and animal Health
4.6.1 Evaluation / decision (MA's)
4.6.2 Evaluation / decision (CT's)
4.6.3 Evaluation / decision CEP's
4.6.4 Evaluation / decision MIA's
4.6.5 Evaluation of withdrawal of CEP on MA


5.0 Suspension or withdrawal of CEP (non GMP)
5.1 Notification by EDQM to Network
5.2 Evaluating the Impact (marketed)
5.3 Evaluating the impact (MA's)
END

Appendix 2: Points to consider when a teleconference is convened by the lead inspectorate authority

1. Introduction

The Union procedure for dealing with serious GMP non-compliance or voiding/suspension of CEPS thus requiring co-ordinated administrative action requires that the lead inspectorate authority should organise a teleconference to give authorities receiving notification of serious GMP non-compliance an opportunity to seek clarifications and to confirm the appropriateness of the recommended actions before they are implemented at Union level.

The purpose of this document is to outline the main points for consideration for the issuing authorities and for the receiving authorities who are participating in the teleconference.

1.1 When to organise a teleconference

A teleconference may be indicated if the manufacturer or importer of the medicinal product is supplying more than one EEA member state and;

Figure: 1. The supervisory risk assessment indicates that urgent interim measures such as a product recall will be necessary.

Figure: 2. The supervisory risk assessment indicates that prohibition of importation or further supply of the concerned medicinal product(s) will be necessary.

Figure: 3. The supervisory risk assessment indicates that measures will have to be taken against the manufacturing/importation or marketing authorisation(s).

Similar considerations apply if the non-compliance concerns a manufacturer of the active pharmaceutical ingredient.

1.2 Practical considerations

The lead inspectorate authority should take the lead in organising and chairing the teleconference. In the case where centrally authorised products are involved, the lead inspectorate authority may agree that EMA organise the TC.

The issuing authority should circulate a draft agenda and participant list in advance of the TC. Each concerned authority should ensure that all meeting participants are identified to the lead inspectorate authority.

The chairman should clearly state and agree with the participating authorities the purpose and objectives of the TC and should clearly summarise the main decisions taken by the participants.

The lead inspectorate authority is responsible for ensuring that minutes/table of actions of the teleconference are taken and agreed with participants. The distribution of the final minutes/table of actions to Member States should be within two weeks of the date of the teleconference

Appendix 3 - Criteria for classification of critical medicinal products Shortages due to GMP non-compliance/quality defects

1. Introduction

GMP non-compliance/quality defects may lead to shortage of a product, if it is decided not to release a batch or even to withdraw batches from the market. Though in general such action based on GMP issues/quality defects is good precautionary practice, there might be situations where withdrawing a product or not releasing it might do more harm to a patient than allowing a product to remain on the market.

The classification of a medicinal product as critical should be performed by CHMP for centrally authorized products (CAPs) or by Member States for non-CAPs taking into account the criteria expressed in this document and supply situations at a national level.

At the moment there is no harmonized approach to such classification, as situations might be different in different countries. Products and/or alternatives may or may not be available and use of products may depend on national preferences. In the following a proposal is made for a more harmonized way of handling the classification of a medicinal product as 'critical'.

The principles set out in this paper may also apply when shortages due to other reasons are encountered, at the Member States' discretion.

2. Criteria for classification

When defining a product as critical, two criteria are of importance: therapeutic use and availability of alternatives.

A. Therapeutic use

The medicinal product is an integral part of the treatment for a disease, which is life-threatening or irreversibly progressive, or without which the patient could be severely harmed.

This could be in acute situations (e.g. emergency situations), or chronic situations/maintenance of stable conditions, or disease with a fatal outcome where the product has been shown to affect the progression of the disease or survival.

B. Availability of alternatives

Even if the product would be used in the situation defined above, it would not be classified as being critical in case appropriate alternatives are available. These could be:

- Alternative manufacturing site for the same product; caveat: manufacturing capacity and technical and regulatory times to switch.
- Different strength/formulations of the same product; caveat: need for formulations suitable for use in special populations.

- Alternative dosing (lower dose/temporary break from drug treatment) or limiting the use to high risk patients could be explored; caveat: this might depend on the expected duration.

Appendix 4 – Decision tree on escalation from national to European level

Shortages due to GMP non-compliance/quality defects

1. Introduction

GMP non-compliance/quality defects may lead to a shortage of a medicinal product, if it is decided that it is necessary to prohibit importation and/or release of a batch or to withdraw batches from the market. Though in general such action based on GMP non-compliance/quality defects is good precautionary practice and at the discretion of the Member States when products are authorized nationally, there might be incidents where it is necessary to elevate the discussion to agree on a harmonized risk management strategy at a Union level in order to protect public health.

The principles set out in this paper may also apply when shortages due to other reasons are encountered, at the Member States' discretion.

2. Problem statement

Supply incidents caused by GMP non-compliance/quality defects may be managed and controlled with the aid of the EU regulatory network incident management plan for medicines for human use.

At the moment there are no standardised criteria in determining whether the EU regulatory network incident management plan for medicines for human use should be initiated for supply shortages due to GMP non-compliance/quality defects.

The current document sets out a decision tree which would facilitate the decision on when such escalation to a European level could be considered.

3. Decision tree

3.1 No escalation to European level is required if:

(a) Shortages are limited to a single member state (although noted that this situation may change over time);

(b) The duration of the shortage is limited and not considered relevant from a clinical point of view (e.g. for vaccines, vaccination may be postponed for a few weeks), although this situation may evolve over time.

3.2 Escalation to a European level may be considered if:

(a) The product is considered to be a critical medicinal product in a member state and there is evidence that indicates that the shortage will affect more than one member state. It is possible that there may be differential supply of GMP compliant/GMP non-compliant product between Member States;

(b) A decision to keep a suspected defective product on the market may have possible safety implications (e.g. sterility is not guaranteed) that may indicate the need for union advice

on appropriate risk minimization measures to be taken to allow continued use of the suspected defective product;

(c) The product at issue is considered to be non-critical but the concern is due to critical GMP non- compliance/quality defects which may affect other products on the union market;

(d) The product is considered to be non-critical but shortages may have an impact on public health (e.g. owing to the number of users or the characteristics of the patient population).

Discussion should always take place on the lowest possible level and only be escalated for further discussion at European level in case there is an interest at Union level identified.

4. Actions at Union level

Once a member state or several Member States have decided that an escalation to Union level is necessary, the following principles should be followed in determining which committee at the agency should take the lead in the assessment and communication strategy. It is proposed that shortages only affecting centrally authorised products (CAPs) as well as shortages affecting both CAPs and non-CAPs are subject to the CHMP's review. Should more than one rapporteurship be affected, a lead rapporteur will be nominated by the committee. Should a shortage only affect non-CAPs, the member state(s) should escalate the issue to the CMD(h) for a harmonised response at Union level. PRAC will be consulted by the committees as necessary.

Appendix 5

Official Letterhead of the National Competent Authority.

'Written confirmation' of API compliance, as defined in Article 46a(2)(b) of Directive 2001/83/EC

The competent authority of *[EU Member State]* wishes to advise the competent authority of *[third country]* that, following an inspection in accordance with Art. 111(7) of Directive 2001/83/EC,

Company name:……..

Site address:……

……

has been found to be **non-compliant** with standards of GMP equivalent to those laid down in Article 47 of Directive 2001/83/EC.

A statement of serious GMP non-compliance has been issued, which is appended to this notice.

[Third country authority] is requested to withdraw previously issued written confirmations of API compliance which fall within the scope of the statement of serious GMP non-compliance. Notification to *[name of supervisory EU authority]* when the manufacturer is considered to have restored compliance equivalent to EU GMP would be appreciated, to assist in scheduling a future EU re-inspection of the site.

Contact details for communications relating to this statement of serious non-compliance are as follows:

Inspection case reference:

……

Name of responsible officer of the EU supervisory authority:

……..

Address:

……

Telephone:

……

Email:

……

Appendix 6: Supervisory risk assessment

Notification by supervisory authority

Issued by:

Inspection reference:

Manufacturer name and address:

Introduction / background:

Brief description of relevant information about the site and background information.

Include what the site is responsible for; what led to the inspection and what the outcome was. Include whether any previous inspections are relevant.

Main inspection findings:

Briefly describe the critical and major deficiencies that have led to the non-compliance statement being issued. Include sufficient detail for complete understanding but consider possible interpretation issues when describing deficiencies.

This section will typically contain more detail than the summary provided in section 3 of the Statement of serious GMP/GDP non-compliance template.

Consider that not everybody reading this information will have expert GMP/GDP technical knowledge.

Concerned medicinal products (if known; list may not be exhaustive):

Provide as much information as possible. Incomplete information should be identified as such.

Include (where relevant, and if known):

- *strength(s) and presentation(s)*
- *pending applications, investigational products*
- *products authorised in other EU Member States*
- *Active substances and any CEPs or ASMFs affected*
- *EudraCT numbers*
- *Identity of other supervisory authorities in the case of medicinal or investigational medicinal products or active substances imported into the Union*
- *RMS(s) and the competent authority(ies) responsible for the marketing authorisation(s)*

Indicate if MRA partners are likely to be affected.

Assessment of main inspection findings on concerned medicinal products:

Describe the impact of the identified GMP/GDP deficiencies on risk to product quality, safety or efficacy. An assessment of impact to clinical trial data validity should be made, if relevant to the GMP/GDP deficiencies (e.g. product mix-ups or failure to properly randomise / blind IMPs).

Have any mitigating actions already been implemented (either formally or informally)? An assessment of the consistent use and effectiveness of these mitigating actions should be provided.

Recommendations:

Any recommendations for action should be commensurate with risk. They should be stated in a manner that takes account of the interests of the Union as a whole, and permits flexibility in decision-making at national and Union level, taking into account product criticality.

- *At the time of drafting, product criticality may not be known for all Member States. Recommendations should accommodate the possibility of critical products as further information becomes available.*

Are there any recommendations towards other National Competent Authorities or EU Committees, for example:

- *If it is believed that there is evidence or significant risk of defective product on the market, any recall recommendations to other Member States should usually be limited to 'consideration of recall following NCA assessment'. Where possible, agree this text with the authority leading quality defect assessments.*
- *Recommendations for prohibition of importation and/or supply*
- *Are NCA assessments required of the product's criticality in the Member States?*
- *Any recommendations for action against marketing authorisation(s) or clinical trial*

The 'assessment of main inspection findings on concerned medicinal products' should provide supporting rationale to recommendations for interim urgent measures and final supervisory actions.

Recommendations are based on the information available at the time of writing, and may be updated in light of further information. Any amendments must be clearly highlighted.

- Interim urgent measures (if applicable):

Include any recommendations to maintain patient safety and/or avoid shortages of critical products in the interim period. This should include the rationale for these actions, with reference to the 'assessment of main inspection findings on concerned medicinal products'.

Recommendations for urgent actions may include recall or prohibition of supply of batches already imported into the Union, but not yet placed on the market.

- Final supervisory actions:

Include any SA proposals for action against EU manufacturing authorisations, or EU importation authorisations in the case of non-compliance at third country manufacturing sites

Any recommendations on final supervisory actions (e.g. action against marketing authorisation(s) or clinical trial authorisation(s)) should be stated in a manner which permits flexibility in decision-making

at national and Union level, taking into account product criticality. Avoid statements that can be interpreted as an instruction, such as "recommendation that MA should be suspended". Instead consider "action against affected MAs should be considered where potential quality defect has greater impact to public health than supply restriction in affected Member State(s)".

Impact on any other active substance manufactured at the same site / CEP considerations (if any):

If CEPs are impacted, ensure that this section is discussed and text agreed with EDQM. If action has not been agreed at the time of publication of the RRA, this can be noted as 'potential impact to CEPs remains under assessment'.

Implications for product supply based on information available to the supervisory authority:

At the time of drafting, product supply and/or criticality information may not be known for all products or Member States. Relevant available information and possible impact on supply following this inspection should be provided, e.g.:

- *Quantity of materials/products available*
- *Number of batches in progress / completed / released*
- *Typical market usage*

Information requested from affected Member States:

A summary of information requested from affected Member States should be listed.

This should be based on the requirements for assessment listed above.

Contact details for responses:

Deadline for responses: