DECISION

No. 8/22.04.2013
on Procedure for dealing with serious GMP non-compliance or voiding/suspension of CEPS thus requiring co-ordinated administrative action

The Scientific Council of the National Agency for Medicines and Medical Devices (NAMMD), established based on Order of the Minister of Health no. 158/18.02.2013, reunited on summons of the President of the National Agency for Medicines and Medical Devices in the ordinary meeting of 22.04.2013, in accordance with Article 12(5) of Government Decision no. 734/2010 on establishment, organisation and operation of the National Agency for Medicines and Medical Devices, as amended, adopts the following

DECISION

Art. 1. – The Procedure for dealing with serious GMP non-compliance or voiding/suspension of CEPS thus requiring co-ordinated administrative action is approved, in accordance with the Annex which is integral part of this Decision.

Art. 2. – On this Decision coming into force, Scientific Council Decision no. 3/2009 on procedure for dealing with serious GMP non-compliance or voiding/suspension of CEPS thus requiring co-ordinated administrative action is repealed.

PRESIDENT
of the Scientific Council
of the National Agency for Medicines and Medical Devices,

Acad. Prof. Dr. Leonida Gherasim

ANNEX
to SCD no. 8/22.04.2013

PROCEDURE

for dealing with serious Good Manufacturing Practice (GMP) non-compliance or voiding/suspension of CEPS thus requiring co-ordinated administrative action

CHAPTER I

Scope

Art. 1. – This procedure is a translation into Romanian and an adaptation of Procedure EMA/INS/GMP/321252/2012 Rev 15 of the European Medicines Agency (EMA) for dealing with serious Good Manufacturing Practice (GMP) non-compliance or voiding/suspension of CEPS thus requiring co-ordinated administrative action.

CHAPTER II

Summary

Art. 2. – A consolidated procedure for dealing with all circumstances of serious GMP non-compliance, whether found at a manufacturing authorisation holder, third country manufacturer or active substance manufacturer is necessary to ensure a coordinated approach to potential risks to public health.

Art. 3. – (1) This document replaces Annex 3 of the Guideline on exchange of Information on Manufacturers and Manufacturing or Wholesale Distribution Authorisations between Competent Authorities in the European Economic Area, approved through Decision of the Scientific Council of the National Medicines Agency (NMA) no. 15/15.06.2007.

(2) The respective Annex deals with serious GMP non-compliance found at a third country manufacturing site where co-ordinated administrative action is necessary.

Art. 4. – Suspension or voiding of a Certificate of the European Pharmacopoeia (CEP) may be a recommended action following an inspection of an active substance manufacturer but this procedure additionally addresses action to be taken in the event of notification by the European Directorate for the Quality of Medicines (EDQM) that a CEP has been voided or suspended for reasons other than serious GMP non-compliance, as the actions and consequences are similar.

Art. 5. – The reporting inspectorate should enter the information on serious GMP non-compliance in EudraGMP, as referred in Article 823(6) of Law no. 95/2006 on healthcare reform, Title XVII - The medicinal product, as amended.

Art. 6. – (1) The procedure requires the inspectorate discovering serious GMP non-compliance to recommend appropriate action, involving other authorities that share supervisory responsibility in developing those recommendations, and to communicate the recommendations to all other authorities in the Community.

(2) Communication with partner authorities in the Mutual Recognition Agreement (MRA) may also be necessary.

Art. 7. – 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 at Community level.

Art. 8. – The Romanian competent authority, the National Agency for Medicines and Medical Devices, must take into account the information on serious GMP non-compliance received and should 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.

Art. 9. – (1) With regard to actions, directly or consequential, against marketing authorisations, the Reference Member State takes the initiative for medicinal products authorised through mutual recognition/decentralised procedure.

(2) The European Medicines Agency (EMA) co-ordinates action for centrally authorised medicinal products.

(3) The NAMMD takes responsibility for marketing authorisations that exist purely at national level.

CHAPTER III
Definitions

Art. 10. – 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 nature that administrative action is necessary to remove a potential risk to public health.

Art. 11. – For the purposes of this procedure, administrative action is one of the actions described in Chapter VII.

CHAPTER IV
Principles

Art. 12. – (1) The GMP inspection report should provide a sound conclusion on overall compliance/non-compliance with GMP principles and Guidelines, as defined in the Order of the Minister of Public Health no. 905/2006 on approval of the Principles and guidelines for good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use and in NAMMD Scientific Council Decision no. 5/2012 on the Guideline on Good Manufacturing Practice.

(2) It is understood that a company can be considered to be in general GMP compliant even if there is a certain degree of non-compliance, fact which, according to the inspector, can be resolved without administrative action being taken.

Art. 13. – (1) Action following the discovery of any non-compliance should be commensurate with the level of risk posed by the non-compliance.

(2) Serious non-compliance by definition requires administrative action to be taken.

Art. 14. – (1) All inspections carried out by the inspection services of any Member States are performed on behalf of the entire Community [1].

(2) 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.

(3) Therefore a mechanism that ensures consistent, co-ordinated action throughout the Community is required.

Art. 15. – 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.

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[1] This includes inspections requested by the European Commission, EMA and EDQM but excludes those performed under contract to WHO. Until further notice serious non-compliance discovered during an inspection on behalf of WHO is not subject to this procedure.

Art. 16. – Exceptionally, where, following proper assessment, specific national factors alter the risk such that the agreed Community 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 Romania, this Member State may, in accordance with Community legislation, decide to take alternative action to that proposed by the Member State revealing the serious GMP non-compliance.

Art. 17. – (1) With regard to actions, directly or consequential, against marketing authorisations, the Reference Member State takes the initiative for medicinal products authorised through mutual recognition/decentralised procedure.

(2) EMA co-ordinates action for centrally authorised medicinal products.

(3) The NAMMD takes responsibility for marketing authorisations that exist purely at national level.

Art. 18. – Unnecessary communication of non-compliance should be avoided in order to make efficient use of the Community alert mechanisms.

CHAPTER V
Scope

Art. 19. – (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 administrative action being taken.

(2) This procedure applies only when the level of non-compliance is such that the inspector concerned recommends that administrative action is taken to remove a potential risk to public health and that recommendation is ratified in accordance with internal national procedures.

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

Art. 20. – (1) This procedure applies to all GMP inspections where serious GMP non-compliance is discovered whether on the territory of the Supervisory Authority or, in third countries, including inspections requested by the manufacturer, European Commission, EMA or EDQM.

(2) It applies to inspections of active substance manufacturers, manufacturers of medicinal products, manufacturers of investigational medicinal products as well as quality control laboratories.

(3) It applies to inspections in third countries covered under the distant assessment procedure.

Art. 21. – In order to avoid unnecessary use of Community alert mechanisms, communication of serious GMP non-compliance in accordance with this procedure should not be initiated when the information and action is of no interest to any other Member State; examples are given in Article 40.

Art. 22. – 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.

Art. 23. – (1) The discovery of serious GMP non-compliance at an active substance manufacturer associated with a CEP and inspected at the request of EDQM may lead to action by EDQM in connection with the CEP, such as suspension or voiding.

(2) However, this procedure must still be invoked in order to ensure coordinated, harmonised action regarding the serious GMP non-compliance itself.

Art. 24. – The procedure also deals with cases where a CEP is declared void by EDQM for reasons unrelated to an inspection outcome as consequential action may be needed, which must be properly implemented and coordinated.

CHAPTER VI
Responsibilities

Art. 25. – (1) Following a GMP inspection, the inspection report must conclude whether the inspected company complies with the principles and guidelines of GMP or not.

(2) If the conclusion is that the inspected company is not GMP compliant, then the inspector concerned should recommend what risk-mitigating action is necessary such as administrative action, including whether a rapid alert is necessary for medicinal products/batches released onto the market and/or whether a prohibition of supply should be enforced.

Art. 26. – With regard to inspections relating to medicinal products and investigational medicinal products, if the authority performing the inspection is not the Supervisory Authority it should involve the Supervisory Authority before issuing any non-compliance report so that any proposed regulatory action can be initially agreed.

Art. 27. – (1) As a national competent authority, the NAMMD should have an internal national procedure to review inspection reports from 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.

(2) According to this procedure, this decision should be reached, and if administrative action is supported, communicated to other competent authorities in accordance with this procedure, within a timeframe appropriate to the potential threat to public health.

Art. 28. – The Supervisory Authority is responsible for taking action against manufacturing authorisation holders under its supervision and/or disciplinary action against Qualified Persons (QPs) connected with manufacturing authorisations under its supervision.

Art. 29. – With regard to marketing authorisations, any recommendations made by the authority reporting the serious GMP non-compliance must take account of the interests of the Community as a whole, regardless as to any specific national considerations as referred to in Article 16 above.

Art. 30. – (1) With regard to actions, directly or consequential, against marketing authorisations, the Reference Member State takes the initiative for medicinal products authorised through mutual recognition/decentralised procedure.

(2) The EMA co-ordinates action for centrally authorised medicinal products.

(3) The NAMMD takes responsibility for marketing authorisations that exist purely at national level.

Art. 31. - Prohibition of supply as a result of GMP non-compliance is action in connection with the marketing authorisation and responsibility should be taken as described in Article 30.

Art. 32. – (1) MRA partners are obliged to notify recipients of GMP certificates exchanged in the context of the MRA when those certificates are withdrawn due to GMP non-compliance.

(2) Since manufacturers themselves may also request GMP certificates to provide to MRA partner authorities, Member States inspectorates should notify all MRA partners when serious GMP non-compliance has been discovered.

Art. 33. – (1) Where an inspection of an active substance manufacturer has been carried out at the request of the EDQM in connection with the CEP scheme and serious GMP non-

compliance is revealed the inspectors involved should bear in mind that they have a dual responsibility.

(2) They should follow the procedures established by EDQM to determine the consequences for the CEP(s) in question, and they have an obligation to the Community to follow this procedure for notifying the serious GMP non-compliance.

(3) Every effort should be made to issue the non-compliance statement at the same time as the notification from EDQM concerning affected CEPs.

Art. 34. – (1) In cases where a CEP has been voided for non-GMP reasons EDQM notifies all national competent authorities using the agreed contact points.

(2) In its notification EDQM should indicate the reasons for voiding in order that authorities receiving the information can decide whether the quality, safety or efficacy of medicinal products already on the market is adversely affected and whether therefore a rapid alert is needed.

Art. 35. – If the authority reporting the serious GMP non-compliance considers it necessary to remove medicinal products or certain batches from the market, it is responsible for issuing the Rapid Alert.

Art. 36. – In the event that a rapid alert is necessary in response to CEP voiding or suspension in the circumstances mentioned in Article 33, 34 and VIII.2, responsibility for issuing the rapid alert is as follows:

- the Reference Member State - for affected medicinal products subject to the Decentralised or Mutual Recognition procedures,
- the EMA will co-ordinate in the same way as a quality defect, for centrally authorised medicinal products,
- For medicinal products subject to national marketing authorisations only, a national recall may suffice. No rapid alert is necessary unless under the specific circumstances it is concluded that a class 1 defect is being handled, or, it is likely that the batches in question are on the market in other Member States.

Art. 37. – Where the agreed action is suspension of a clinical trial each National Competent Authority authorising the trial in question should make appropriate entry into the EudraCT database.

CHAPTER VII
Types and consequences of administrative action

Art. 38 – (1) Some actions may lead to consequential actions. For instance, if a manufacturing authorisation is revoked or suspended or a CEP is voided or suspended it will have an impact on one or more marketing authorisations.

(2) Serious GMP non-compliance found at an active substance manufacturer means 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 authorisation or QPs connected with it.

(3) One or more of the following actions is/are possible.

(4) It is stressed that these are options and Romania should take measures that are the most appropriate to the specific circumstances:

VII.1 Community notification of GMP non-compliance

Art. 39. – Apart from the situations described under Art. 40, the information related to non-compliance with GMP should be introduced in the EudraGMP database.

Art. 40 – (1) Community notification of serious GMP non-compliance is not necessary where the action to be taken is of no interest to any other Member State. Examples include:

- Action restricted to disciplining a QP;
- Action restricted to refusal to grant a manufacturing authorisation or application to vary a manufacturing authorisation;
- For manufacturers located in the Community, action limited to the issue of a restricted GMP certificate without corresponding action being deemed necessary, at the time, with regard to the relevant manufacturing authorisation.

(2) Note: Such action would allow continued manufacture but would put pressure on the manufacturing authorisation holder concerned to take corrective action before taking steps against the manufacturing authorisation are taken, and the remainder of this procedure invoked. This approach is not suitable for manufacturers located in third countries since the close level of supervision implied is not feasible. Furthermore the GMP certificate for a third country manufacturer carries more weight within the Community regulatory system than it does for manufacturers subject to a Community manufacturing authorisation, where the manufacturing authorisation is the primary means of confirming GMP compliance.

VII.2 Withdrawal of GMP certificate or Issue of GMP certificate with restricted scope

Art. 41. – (1) Existing valid GMP certificates with conflicting information will be superseded and should therefore be withdrawn according to Decision no. 22/28.09.2007 on approval of the Guideline for the procedure for the issue and update of GMP certificates.

(2) In some 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.

Art. 42. – (1) A GMP certificate may be restricted for reasons other than serious GMP non-compliance, for example where a third country manufacturer is only partly inspected.

(2) However, if a certificate is restricted because of serious non-compliance then this procedure must be followed and a notification of non-compliance entered into EudraGMP, unless Article 40 applies.

VII.3 Actions taken against a manufacturing/importing authorisation

Art. 43. – Except under the specific circumstances described in section 6.1.2, consequential administrative action will be required for any directly affected manufacturing authorisation; otherwise there will be an unintentional inconsistency in the information available in the EudraGMP database.

Art. 44. – The actions against a manufacturing authorisation may involve the following:

a. Refusal to grant a manufacturing authorisation or an application to vary a manufacturing authorisation.

b. Total or partial suspension or revocation of the manufacturing authorisation.

VII.4 Voiding or suspension of CEP

Art. 45. – (1) The EDQM is responsible for actions directly involving CEPs.

(2) However, if a CEP is voided, marketing authorisations depending solely on the CEP are invalid and should be suspended until the dossier is supplemented through variation with new information on the active substance.

(3) If the grounds for voiding the CEP are related to GMP non-compliance then an alternative active substance manufacturer would need to 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 procedure.

Art. 46 – (1) CEPs may be voided for reasons unrelated to inspections, for example failure to fulfil critical commitments.

(2) Upon such notification by EDQM, the NMA should establish whether it has issued national marketing authorisations that depend on the CEP(s) in question, and, where relevant, whether Romania is a Reference Member State.

(3) The EMA will assess any impact on centrally authorised medicinal products.

Art. 47. – (1) Marketing authorisations depending on the CEP are invalid and should be suspended until the dossier is supplemented through variation with new information on the active substance and should therefore be suspended, unless an alternative source of active substance is authorised which is unaffected by the voided CEP.

(2) The Reference Member State should take the initiative in taking action against marketing authorisations subject to the mutual recognition or decentralised procedures.

(3) The EMA will co-ordinate the actions relating to centrally authorised medicinal products.

(4) The NAMMD takes action against the marketing authorisation in the case of medicinal products authorised solely on a national basis.

VII.5 Actions related to marketing authorisations

Art. 48 – (1) Actions that can be taken include refusal to grant a marketing authorisation or application for variation, suspension or withdrawal.

(2) A marketing authorisation holder may also decide to withdraw a marketing authorisation voluntarily.

Art. 49. – (1) In the context of this procedure actions against marketing authorisations may be a consequence of action against the manufacturing authorisation or as a result of suspension or voiding of a CEP.

(2) It is possible however that the most appropriate course of action is the one taken against the marketing authorisation(s) alone; for example, a marketing authorisation listing a seriously non-compliant third country manufacturing site may need to be suspended or revoked unless an alternative manufacturing site is already authorised.

(3) A seriously non-compliant third country manufacturing site may need to be removed from a marketing authorisation through a variation.

Art. 50. – (1) 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 safeguard public health.

(2) If the suspension or withdrawal of the manufacturing authorisation is partial then not all marketing authorisations listing the site will be affected.

Art. 51. – In this case, the Reference Member State, for medicinal products subject to decentralised or mutual recognition procedures, the EMA in the case of medicinal products authorised through centralised procedure, or the NAMMD in the case of medicinal products authorised on a national basis only takes action against the marketing authorisation.

VII.6 Impact on clinical trials

Art. 52. – (1) If serious GMP non-compliance is discovered at the manufacturer 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 reporting inspectorate.

(2) Trials may need to be suspended.

(3) Furthermore in some cases the results of completed trials may be doubted. Interruption, suspension or prohibition of trial must be entered into EudraCT.

Art. 53. – (1) The authority that carried out the inspection should involve the sponsor as well as the manufacturer in order to identify all affected trials.

(2) If trials are prematurely terminated appropriate entries in EudraCT must be made.

VII.7 Rapid Alert

Art. 54. – Based on the information in the inspection report the authority reporting the serious GMP non-compliance should decide, in addition to any other action, whether or not it is necessary to take action with respect to batches of affected medicinal product(s) already on the market or being used in clinical trials.

Art. 55. - For CEP voiding by EDQM that is unrelated to the outcome of an inspection, the Reference Member State (or EMA in the exceptional case that centrally authorised medicinal products authorised are affected) should recommend whether any batches should be recalled and invoke any Rapid Alert based on the information provided by EDQM on the reasons for voiding or suspension in its notice of voiding/suspension or, if necessary, following discussion with EDQM.

Art. 56. – In the context of this procedure responsibility for issuing a rapid alert is outlined in Article 36.

VII.8 Prohibition on supply

Art. 57. – Based on the information in the inspection report the authority reporting the serious GMP non-compliance should decide, in addition to any other action, whether or not to recommend a prohibition on supply to prevent medicinal products or batches from being released to the market or for use in clinical trials.

VII.9 Disciplinary measures against the Qualified Person(s)

Art. 58. – (1) This action can be taken by the Supervisory authority if deemed appropriate. In some cases it may be the only required action.

(2) If this is the only action taken there is no impact on other Member States (see Article 40).

CHAPTER VIII
Communication

VIII.1 Serious GMP non-compliance

Art. 59. – Notification of serious GMP non-compliance should take place after national procedures for dealing with adverse inspection reports have been followed and the action recommended by the inspector ratified or alternative action decided upon.

Art. 60 – (1) In principle, unilateral action by one Member State should be avoided, unless justified.

(2) In order to facilitate co-ordinated action at Community level, notification of serious GMP non-compliance should be made prior to the execution of any action.

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

- the identity of Member States with medicinal products directly affected by inspection findings;
- where relevant, the Reference Member State(s);
- whether centrally authorised medicinal products are involved;
- the identity of other Supervisory Authorities in the case of medicinal or investigational medicinal products;
- for investigational medicinal products the EudraCT trial reference numbers should be identified;
- In the case of active substance manufacturer whether CEPs are affected in addition to marketing authorisations directly affected.

(4) The authority that discovers the non-compliance should involve the manufacturer concerned, the importer and trial sponsor as appropriate to gather this information.

(5) It may be necessary to issue the notice of non-compliance without complete information if the risk to patient health is considered particularly severe.

Art. 61. – Where there is more than one Supervisory Authority they should all be consulted by the reporting authority on proposed actions before transmission of the non-compliance information.

Art. 62. – (1) The agreed Community GMP non-compliance format should be used to report the non-compliance information to the EudraGMP database.

(2) The rapid alert distribution list should be used for this purpose.

Art. 63. – The GMP non-compliance notification should explain the nature of any proposed action, or where justified, action already taken.

Art. 64. – (1) Any further communication with the issuing authority requesting clarification the non-compliance or providing relevant data, should be made via EudraGMP.

(2) All these questions and answers will then be available to all National Competent Authorities.

Art. 65. – (1) Where relevant, a contact telephone number should be given in the 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.

(2) The EDQM should be invited to join the teleconference if a CEP is affected.

Art. 66. – (1) The outcome of the teleconference, if held, should be communicated in a follow-up message to confirm that the recommended action in the initial notification was agreed or to communicate any other agreed Community action.

(2) EudraGMP will be used for this.

Art. 67. – 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 serious non-compliance, unless it is clear that no CEPs are affected.

Art. 68. – (1) MRA partners are obliged to notify recipients of GMP certificates issued in the context of the MRA withdrawing those certificates if serious non-compliance is discovered.

(2) MRA partners given access to EudraGMP will be notified automatically of GMP non-compliance statements placed into the database.

Art. 69. – (1) The issuing authority may amend the non-compliance information entered in the EudraGMP database, if necessary.

(2) Any new modification of the non-compliance information should be distributed to the rapid alert distribution list.

VIII.2 Voiding of CEPs for reasons other than GMP non-compliance

Art. 70. – (1) In cases where a CEP has been voided for non-GMP reasons EDQM notifies all national competent authorities using the agreed contact points.

(2) In its notification, the EDQM should indicate the reasons for voiding in order that authorities receiving the information can decide whether the quality, safety or efficacy of medicinal products already on the market is adversely affected and whether therefore a rapid alert is needed.

(3) Responsibilities are defined in Art. 36.

CHAPTER IX
Post-communication procedure: Serious GMP non-compliance

Art. 71. – (1) On receipt of a form notifying serious GMP non-compliance, either by fax or through EudraGMP, the NAMMD should check whether nationally authorised medicinal products in Romania are affected, and whether Romania is a Reference Member State for any affected medicinal products, seeking assistance from the inspectorate carrying out the inspection, if different, and the manufacturer(s) concerned as needed.

(2) If either applies, they should join the teleconference if there is to be one.

(3) 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.

(4) In the case of action against marketing authorisations subject to the decentralised/mutual recognition procedures, the Reference Member State should take the initiative in following the recommendations of the Authority reporting the non-compliance.

(5) The EMA will coordinate action relating to centrally authorised medicinal products.

Art. 72. – Disagreement with the actions proposed, if not resolved at the teleconference, should be dealt with through procedures established in accordance with Article 839 of Law no. 95/2006 on healthcare reform, Title XVII - The medicinal product, as amended.

Art. 73. – In the case of actions proposed for marketing authorisations subject to the Decentralised or Mutual Recognition procedures, the Co-ordination Group for Mutual Recognition and Decentralised Procedures [CMD (h)] may decide to discuss the coordination of actions at a meeting of the relevant group prior to implementation.

Art. 74. – (1) Exceptionally, where, following proper assessment, specific national factors alter the risk such that the agreed Community 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 Romania, this 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.

(2) In such cases, in line with Article 839 of Law no. 95/2006 on healthcare reform, Title XVII - The medicinal product, as amended, it is Romania’s duty to notify the EMA and the European Commission.

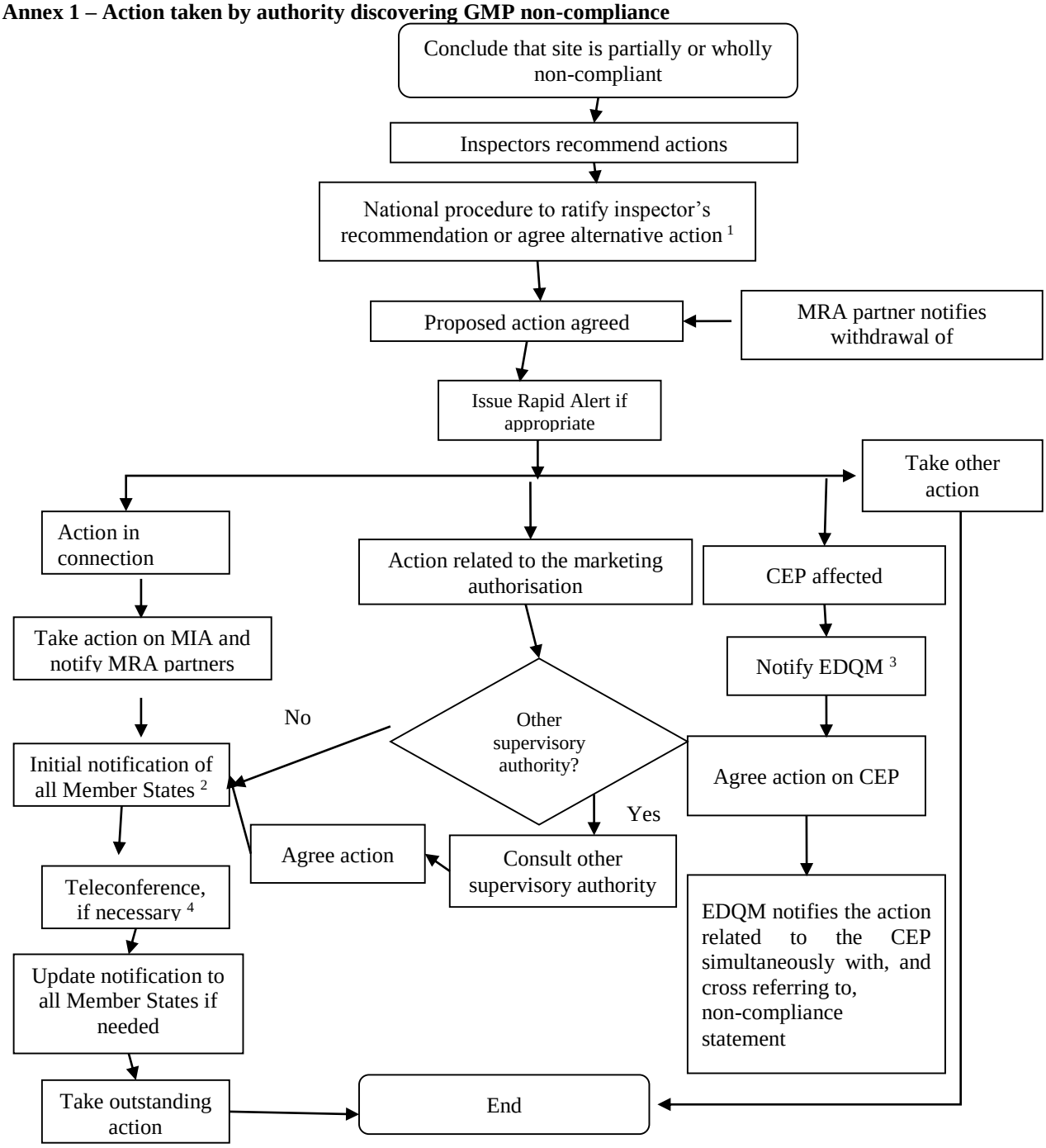
(3) The Supervisory Authority or Reference Member State may find itself in this position but should nevertheless fulfil its responsibilities under chapter VI.

CHAPTER X
Legal References

- Law no. 95/2006 on healthcare reform, Title XVII - The medicinal product, as amended – Chapter XII Supervision and sanctions.

- Law no. 95/2006 on healthcare reform, Title XVII-The medicinal product, as amended – Chapter XIII General provisions.
- Regulation (EC) no. 726/2004 of the European Parliament and of the Council laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, Title II Chapter 2 Supervision and Penalties.
- The Compilation of Community Procedures for Inspections and the Exchange of Information, published by the European Commission [Article 4 of Order of the Ministry of Public Health no. 905/2006 on approval of Principles and guidelines for good manufacturing practice in respect of medicinal products for human use and investigational medicinal products (IMPs) for human use].

Annex 1 – Action taken by authority discovering GMP non-compliance



*MIA = Manufacturing/Importing authorisation

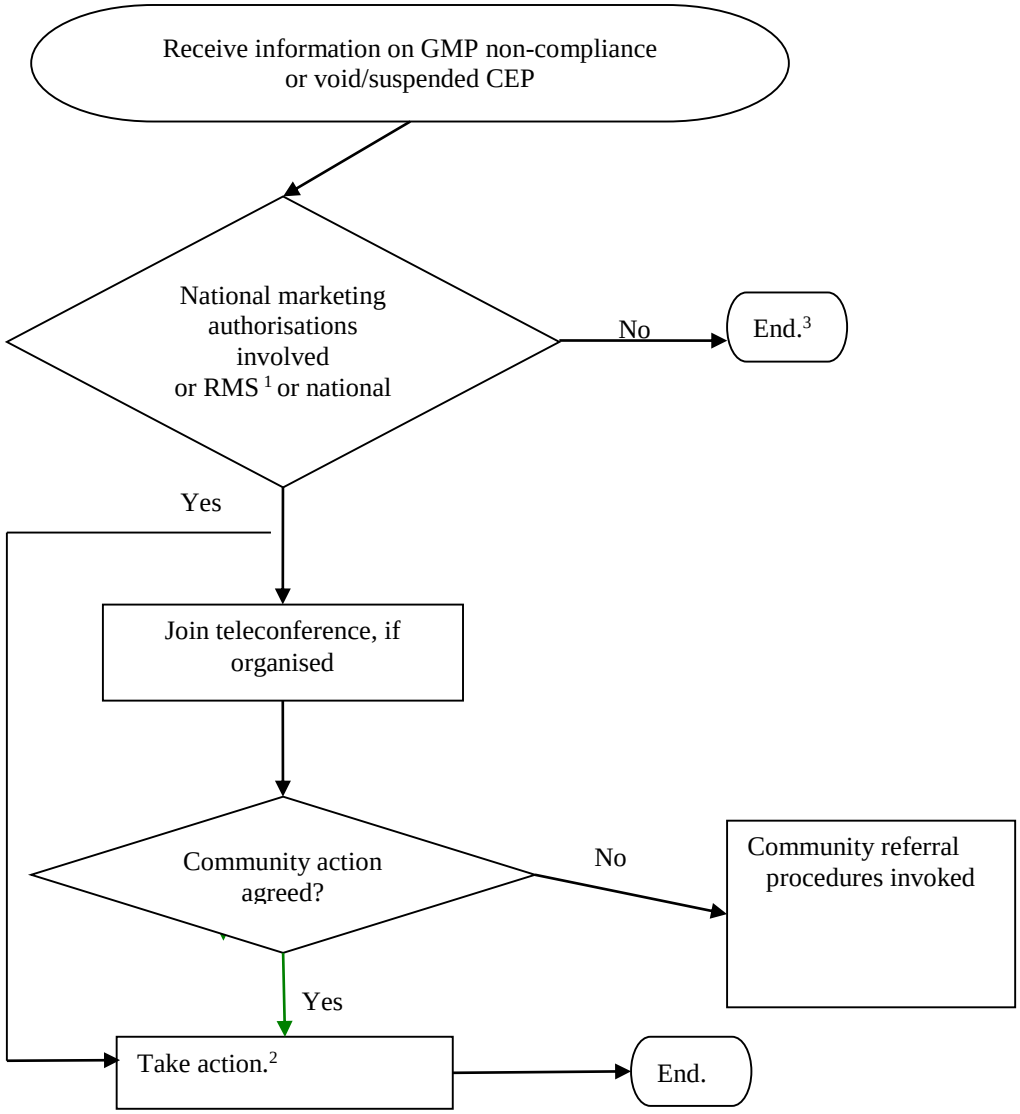
[1] If action against marketing authorisations is considered, the action ratified is that regarded as appropriate for the Community. If the reporting authority is not the Supervisory Authority the Supervisory Authority must be involved in the decision process.

[2] Via EudraGMP

[3] This is the starting point for CEPs voided for reasons unrelated to a GMP inspection.

[4] If a CEP is involved EDQM is invited to join. If desired, coordination of action in respect of marketing authorisations subject to the mutual recognition or decentralised procedures may be discussed at the next meeting of CMD(h).

Annex 2 – Action by Authorities following receipt of information of GMP non-compliance



[1]EMA co-ordinates action for centrally authorised medicinal products
[2]Reference Member States (RMSs) should take the agreed action at Community level
[3]Notwithstanding appropriate responses to consequential rapid alerts or other consequential actions agreed at Community level

Annex 3

(LETTERHEAD OF COMPETENT AUTHORITY)

Report No: _ _ _/_ _ _/_ __/_ _

STATEMENT OF NON-COMPLIANCE WITH GMP

Exchange of information between National Competent Authorities (NCAs) of the EEA following the discovery of serious GMP non-compliance at a manufacturer[2]

Part 1

Issued following an inspection in accordance with Art. 111(7) of Directive 2001/83/EC, Art. 80(7) of Directive 2001/82/EC or Art. 15 of Directive 2001/20/EC.*

The competent authority of.....*[Member State]* confirms the following:

The manufacturer

.....

Site address

.....

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on …../...…/..…. *[date]*, it is considered that **it does not comply with the Good Manufacturing Practice** requirements referred to in the principles and guidelines of Good Manufacturing Practice laid down in Directive 2003/94/EC/Directive 91/412/EEC/ the principles of GMP for active substances referred to in Article 47 of Directive 2001/83/EC / Article 51 of Directive 2001/82/EC / an appropriate level of GMP as referred to in Article 46(f) of Directive 2001/83/EC*

[2] The statement of non-compliance referred to in paragraph 111(7) of Directive 2001/83/EC and 80(7) of Directive 2001/82/EC, as amended, is also applicable to importers.

Part 2

☐ Human Medicinal Products*

☐ Human Investigational Medicinal Products*

1 NON-COMPLIANT MANUFACTURING OPERATIONS- MEDICINAL PRODUCTS *	
1.1	*Sterile Products*
	1.1.1 Aseptically prepared (processing operations for the following dosage forms) 1.1.1.1 Large volume liquids 1.1.1.2 Lyophilisates 1.1.1.3 Semi-solids 1.1.1.4 Small volume liquids 1.1.1.5 Solids and implants 1.1.1.6 Other aseptically prepared products <free text>
	1.1.2 Terminally sterilised (processing operations for the following dosage forms) 1.1.2.1 Large volume liquids 1.1.2.2 Semi-solids 1.1.2.3 Small volume liquids 1.1.2.4 Solids and implants 1.1.2.5 Other terminally sterilised prepared products <free text>
	1.1.3 Batch certification
1.2	**Non-sterile products**
	1.2.1 Non-sterile products (processing operations for the following dosage forms) 1.2.1.1 Capsules, hard shell 1.2.1.2 Capsules, soft shell 1.2.1.3 Chewing gums 1.2.1.4 Impregnated matrices 1.2.1.5 Liquids for external use 1.2.1.6 Liquids for internal use 1.2.1.7 Medicinal gases 1.2.1.8 Other solid dosage forms 1.2.1.9 Pressurised preparations 1.2.1.10 Radionuclide generators 1.2.1.11 Semi-solids 1.2.1.12 Suppositories 1.2.1.13 Tablets 1.2.1.14 Transdermal patches 1.2.1.15 Other non-sterile medicinal product <free text >
	1.2.2 Batch certification
1.3	**Biological medicinal products**
	1.3.1 Biological medicinal products 1. Blood products 2. Immunological products 3. Cell therapy products 4. Gene therapy products 5. Biotechnology products 6. Human or animal tissue extracted products 7. Tissue engineered products 8. Other biological medicinal products <free text >

	1.3.2 Batch certification (list of product types) 1. Blood products 2. Immunological products 3. Cell therapy products 4. Gene therapy products 5. Biotechnology products 6. Human or animal tissue extracted products 7. Tissue engineered products 8. Other biological medicinal products <free text >
1.4	**Other products or manufacturing activity**
	1.4.1 Manufacture of: 1.4.1.1 Herbal products 1.4.1.2 Homoeopathic products 1.4.1.3 Other <free text >
	1.4.2 Sterilisation of active substances/excipients/finished product: 1.4.2.1 Filtration 1.4.2.2 Dry heat 1.4.2.3 Moist heat 1.4.2.4 Chemical 1.4.2.5 Gamma irradiation 1.4.2.6 Electron beam
	1.4.3 Others <free text>
1.5	Packaging
	1.5.1 Primary packing 1.5.1.1 Capsules, hard shell 1.5.1.2 Capsules, soft shell 1.5.1.3 Chewing gums 1.5.1.4 Impregnated matrices 1.5.1.5 Liquids for external use 1.5.1.6 Liquids for internal use 1.5.1.7 Medicinal gases 1.5.1.8 Other solid dosage forms 1.5.1.9 Pressurised preparations 1.5.1.10 Radionuclide generators 1.5.1.11 Semi-solids 1.5.1.12 Suppositories 1.5.1.13 Tablets 1.5.1.14 Transdermal patches 1.5.1.15 Other non-sterile medicinal products <free text >
	1.5.2 Secondary packing
1.6	Quality control testing
	1.6.1 Microbiological: sterility
	1.6.2 Microbiological: non-sterility
	1.6.3 Chemical/Physical
	1.6.4 Biological

2 NON-COMPLIANT IMPORTATION OPERATIONS*

2.1	**Quality control testing of imported medicinal products**
	2.1.1 Microbiological: sterility
	2.1.2 Microbiological: non-sterility
	2.1.3 Chemical/Physical
	2.1.4 Biological
2.2	Batch certification of imported medicinal products
	2.2.1 *Sterile Products* 2.2.1.1 Aseptically prepared 2.2.1.2 Terminally sterilised
	2.2.2 Non-sterile products
	2.2.3 Biological medicinal products 2.2.3.1 Blood products 2.2.3.2 Immunological products 2.2.3.3 Cell therapy products 2.2.3.4 Gene therapy products 2.2.3.5 Biotechnology products 2.2.3.6 Human or animal extracted products 2.2.3.7 Tissue engineered products 2.2.3.8 Other biological medicinal products <free text >
2.3	**Other importation activities**
	2.3.1 Site of physical importation
	2.3.2 Importation of intermediate which undergoes further processing
	2.3.3 Other <free text>

Any restrictions or clarifying remarks related to the scope of this statement*:

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3 MANUFACTURING OPERATIONS - ACTIVE SUBSTANCES Active Substance(s):	
3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.1 Manufacture of active substance intermediates *3.1.2 Manufacture of crude active substance* *3.1.3 Salt formation / Purification steps : <free text> (e.g. crystallisation)* *3.1.4 Other <free text>*
3.2	**Extraction of Active Substance from Natural Sources**
	3.2.1 Extraction of substance from plant source *3.2.2 Extraction of substance from animal source*

	3.2.3 Extraction of substance from human source *3.2.4 Extraction of substance from mineral source* *3.2.5 Modification of extracted substance <specify source 1,2,3,4>* *3.2.6 Purification of extracted substance <specify source 1,2,3,4 >* *3.2.7 Other <free text>*
3.3	**Manufacture of Active Substance using Biological Processes**
	3.3.1 Fermentation *3.3.2 Cell Culture <specify cell type> (e.g. mammalian / bacterial)* *3.3.3 Isolation / Purification* *3.3.4 Modification* *3.3.5 Other <free text>*
3.4	**Manufacture of sterile active substance (sections 3.1, 3.2, 3.3 to be completed as applicable)**
	3.4.1 Aseptically prepared *3.4.2 Terminally sterilised*
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps < specify > (e.g. drying, milling / micronisation, sieving) *3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance)* *3.5.3 Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)* *3.5.4 Other <free text> (for operations not described above)*
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing *3.6.2 Microbiological testing (excluding sterility testing)* *3.6.3 Microbiological testing (including sterility testing)* *3.6.4 Biological Testing*

4. OTHER ACTIVITIES- ACTIVE SUBSTANCES
<free text>

Any restrictions or clarifying remarks related to the scope of this statement*:

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Part 3

1. Nature of non-compliance

<free text > .....

.....

2. Action taken/proposed by the NCA

☐ Suspension/Variation/Revocation* of the manufacturing authorisation no. …… in full/in part*

<free text > .....

.....

☐ Restriction of current valid GMP certificate no. .....

<free text > .....

.....

☐ Suspension/Revocation/Requested variation/ Refusal to grant * of Marketing Authorisation(s)

<free text> .....

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☐ Recall of batches already released (separate Rapid Alert to follow)

<free text > .....

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☐ Prohibition of supply

<free text >.....

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☐ Suspension or voiding of CEP (action to be taken by EDQM)

<free text > .....

.....

☐ Suspension of clinical trials

<free text > .....

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☐ Others <free text >

<free text > .....

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3. Additional comments

<free text > .....

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Teleconference Date		**Teleconference Time (CET)**		**Dial in no.**	
Products manufactured at site, if known	**Product**	**Dosage Form**	**Reference Member State, National or EMEA**		
Human medicinal product(s)					
Investigational medicinal product(s)	**EudraCT nos.**				

…../...…/.....… *[date]*

Name and signature of the authorised person of the Competent Authority of *[country]*[3]

[Name, title, national authority, phone & fax numbers in case of enquiries]

[3] The signature, date and contact details should appear on each page of the non-compliance document.