DECISION

No. 9/22.04.2013

on Procedure for dealing with serious good manufacturing practice (GMP) non-compliance information originating from third country authorities or international organisations

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

Sole article. – The Procedure for dealing with serious Good Manufacturing Practice (GMP) non-compliance information originating from third country Authorities or international organisations is approved, in accordance with the Annex which is integral part of this Decision.

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

Acad. Prof. Dr. Leonida Gherasim

ANNEX
to SCD no. 9/22.04.2013

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

CHAPTER I

Introduction

Art. 1. – This Procedure is a translation into Romanian and an adaptation of the procedure for dealing with serious GMP non-compliance information originating from third country authorities or international organisations included in the compilation of community procedures EMA/INS/GMP/321252/2012 Rev 15 issued by the European Medicines Agency (EMA).

CHAPTER II
Summary

Art. 2. – A consolidated procedure for dealing with all circumstances of serious GMP non-compliance information originating from third country authorities and international organisations is necessary to ensure a coordinated approach to potential risks to public health. Information may refer to API, finished product or IMP manufacturers and/or QC labs located either in the EU/EEA or in a third country.

Art. 3 – This document supplements the procedure in the Compilation of Community Procedures (CoCP) for dealing with serious Good Manufacturing Practice (GMP) non-compliance (transposed into national legislation by NAMMD Scientific Council Decision no. 3/2009), with regard to the receipt, dissemination and initial assessment of serious GMP non-compliance notifications which originate from third country (non-EU, non-MRA) authorities or international organisations (e.g. WHO).

Art. 4 – This procedure requires the Competent Authorities in the EEA involved in the receipt and coordination of serious GMP non-compliance notifications to disseminate relevant information to all other authorities in the Community in a timely manner, to enable the scope and impact of the notification to be confirmed, and subsequent recommendations for action to be made.

Art. 5 – Communication with authorities of those countries with which the Community has made appropriate arrangements on GMP (e.g. MRA) may also be necessary.

CHAPTER III
Definitions

Art. 6 – For the purposes of this procedure, serious GMP non-compliance is non-compliance with GMP that in the opinion of the reporting authority is of such nature that administrative action is necessary to remove a potential risk to public health. It should be noted that authorities in Third Countries issuing information may not share the same understanding.

CHAPTER IV
Principles

Art. 7 – (1) Notification of serious GMP non-compliance from a third country authority or an international organisation is to be assessed to determine the impact with respect to medicinal products supplied to the Community. It is possible that the detailed GMP non-compliances identified in the notification may have limited or no impact on EU products, e.g.:

- in cases where the issues relate to facilities or products which are not involved in EU supply, or
- where the non-compliances do not relate to GMP principles and guidelines as defined in the relevant Directives and as interpreted in Guidelines on GMP published by the European Commission in Eudralex Volume 4, or
- Where the impact of the identified non-compliances, as interpreted in Guidelines on GMP published in Eudralex Volume 4, does not pose a significant risk to the quality or safety of products for EU supply.

(2) Therefore, it is important to determine the degree of Community impact as soon as possible following the initial notification.

Art. 8 – Action following the notification of any serious GMP non-compliance must be commensurate with the level of risk. Confirmation of serious non-compliance with the principles and guidelines of EU GMP by definition requires administrative action to be taken. Notification of GMP deficiencies which do not require administrative action is recorded in the relevant Supervisory Authority's model for risk based inspection planning, in accordance with CoCP.

Art. 9 – The notification of a serious GMP non-compliance may have implications not only for the Member State receiving the notification but also for other, possibly all, Member States. Therefore, a mechanism that ensures consistent, co-ordinated action throughout the Community is important, even though the final outcome may differ based on specific national factors.

CHAPTER V
Scope

Art. 10 – This procedure relates to the receipt, dissemination and initial assessment of the information relating to serious GMP non-compliance received from third country authorities. If, following assessment of the notification, the nature and severity of non-compliance is considered to pose a potential risk to public or animal health, coordinated administrative action applicable to the situation is to be considered in accordance with the detailed guidance provided in CoCP. Procedures require the adherence to timelines that ensure that serious non-compliance is dealt with in a timely manner.

Art. 11 – This procedure applies to all notifications of serious GMP non-compliance discovered by a third country authority or international organisations either in the territory of an EEA Supervisory Authority or in third countries. It applies to inspections of active substance manufacturers, manufacturers or importers of medicinal products, manufacturers or importers of investigational medicinal products as well as quality control laboratories.

Art. 12 – Notifications of serious non-compliance with Good Practice in the case of human blood, blood components or tissues, when used as a starting material in medicinal products, may also follow this procedure.

Art. 13 – 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.

CHAPTER VI
Procedure and responsibilities

Art. 14 – Receipt of third country Authority notification

14.1 A Member State who receives notification from a third country authority relating to serious GMP non-compliance at a manufacturer must ensure that sufficient information is obtained to permit an assessment of Community impact. Information is collected using the format given in Annex 1. The information to be recorded in this template includes:

- Contact details of single point of contact (SPoC) from the notifying authority;
- Manufacturer name and address;
- SPoC for manufacturer;
- Product-related information:
    - Human / Veterinary / IMP / API / export only;
    - Products / dosage forms / buildings / lines affected;
    - Centralised / DC / MRP / national marketing authorisations / products not subject to a MA;
- Non-compliance issues:
    - Serious EU GMP non-compliance;
    - Serious third country GMP non-compliance.

14.2 The Member State which receives the initial notification may need to request further information from either the notifying third country authority, or the manufacturing site to which the notification refers, in order to ensure that the original information can be validated, and that sufficient information is obtained to permit an impact assessment in all Member States.

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

14.4 If the third country authority notification refers to a site in a third country, the Member State who receives the initial non-compliance notification is responsible for dissemination to all EU Member States and EMA, using the rapid alert single point of contact (SPoC) list[1].

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

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

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

[1] Without prejudice to any confidentiality arrangements

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

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

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

14.10 If additional information becomes available during the process which indicates that a change in coordinating Competent Authority is appropriate (e.g. due to additional information on affected products), this is agreed between the initial coordinator and the proposed new coordinator. Contact details of the new coordinator are to be sent to the concerned Member States, and the contacts listed in section 14.8 above. Care is taken to ensure that a change in coordinator is made only where absolutely necessary and are clearly communicated, in order to avoid confusion or delays in the assessment process.

14.11 The coordinating Competent Authority continues to gather further information and clarification on the detailed inspection findings, impact on EU GMP and public health. Coordination of issues with Marketing Authorisation Holders (MAHs) may be required at this point, in order to determine potential impact on maintaining supplies. In cases where product is certified to the market by the holder of a Manufacturing and Import Authorisation who is not the MAH, information is also obtained from the Qualified Person. Following collation of detailed GMP non-compliance and product related information, a risk assessment is performed to determine the actions to be taken. Further guidance on the administrative actions available for consideration is described in CoCP.

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

14.13. If the initial dissemination of information by the Member State which received the initial notification indicated that more than one Member State is affected by the notification of serious GMP non-compliance, a contact telephone number is to be provided by the coordinating Competent Authority, together with a proposed time and date for a teleconference in which all affected Member States can join. This will assist in ratification of proposed administrative action. The European Directorate for the Quality of Medicines (EDQM) is

invited to join the teleconference if a Certificate of the European Pharmacopoeia (CEP) is affected.

14.14 The coordinating Competent Authority is responsible for communicating the agreed administrative actions to the affected Member States using the template provided in Annex 1.

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

ANNEX 1

(LETTERHEAD OF COMPETENT AUTHORITY)

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

STATEMENT OF NON-COMPLIANCE WITH GMP

Exchange of information between National Competent Authorities (NCAs) of the EEA following notification of serious GMP non-compliance at a manufacturer.

Part 1

Issued by the competent authority of …….*[Member State]* following notification from a third country authority or international organisation in accordance with reference to CoCP here.

……..*[third country authority / International organisation name]* reports the following:

The manufacturer…….……..

Site address……
……...

DUNS Number (if known)…….....…….

Site contact name, title, email, phone and fax number ……..

Third country authority / international organisation contact name, title, email, phone and fax number
……..

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……*[third country / international GMP standards or regulations used for assessment]* , relating to medicinal products/active substances/excipients*

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 1.3.1.1 Blood products 1.3.1.2 Immunological products 1.3.1.3 Cell therapy products 1.3.1.4 Gene therapy products 1.3.1.5 Biotechnology products 1.3.1.6 Human or animal extracted products 1.3.1.7 Tissue engineered products 1.3.1.8 Other biological medicinal products <free text >
	1.3.2 Batch certification (list of product types) 1.3.2.1 Blood products 1.3.2.2 Immunological products 1.3.2.3 Cell therapy products 1.3.2.4 Gene therapy products 1.3.2.5 Biotechnology products 1.3.2.6 Human or animal extracted products 1.3.2.7 Tissue engineered products 1.3.2.8 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
	1.4.1 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 notification*:

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*

Part 3

1. Nature of non-compliance (check all relevant boxes)	
☐ Analytical validation	☐ Housekeeping - cleanliness, tidiness
☐ Batch release procedures	☐ In-process controls - control and monitoring of production operations
☐ Calibration of measuring and test equipment	☐ Intermediate and bulk product testing
☐ Calibration of reference materials and reagents	☐ Investigation of anomalies
☐ Cleaning validation	☐ Line clearance, segregation and potential for mix-up
☐ Complaints and product recall	☐ Personnel issues: Duties of key personnel
☐ Computerised systems - documentation and control	☐ Personnel issues: Hygiene/Clothing
☐ Computerised systems - validation	☐ Personnel issues: Training
☐ Contamination, chemical/physical - potential for	☐ Process validation
☐ Contamination, microbiological - potential for	☐ Production planning and scheduling
☐ Design and maintenance of equipment	☐ Regulatory issues: Non-compliance with manufacturing authorisation
☐ Design and maintenance of premises	☐ Regulatory issues: Non-compliance with marketing authorisation
☐ Documentation - manufacturing	☐ Regulatory issues: Unauthorised activities
☐ Documentation - quality system elements/procedures	☐ Sampling - procedures and facilities
☐ Documentation - specification and testing	☐ Self-inspection
☐ Environmental control	☐ Starting material and packaging component testing
☐ Environmental monitoring	☐ Status labelling - work in progress, facilities and equipment
☐ Equipment qualification	☐ Sterility Assurance
☐ Finished product testing	☐ Supplier and contractor audit and technical agreements
☐ Handling and control of packaging components	☐ Warehousing and distribution activities

2. Action taken/proposed* by the third country authority or International organisation: ☐ Suspension, variation, revocation* of the manufacturing site approval in full or in part ☐ Withdrawal, of current valid GMP certificate / statement ☐ Suspension, Revocation or Requested Variation* of product registrations ☐ Recall of batches already released ☐ Prohibition of supply ☐ Suspension of clinical trials ☐ Others <free text >
3. Additional comments

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

Name of the authorised person of the Competent Authority of …….....…….*[Member State]*

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

…../...…/.....… *[date]*

(*): delete that which does not apply.