DECISION

No. 22/28.09.2007

on approval of Guideline on the issue and update procedure of Good Manufacturing Practice certificates

The Scientific Council of the National Medicines Agency,
set up based on Minister of Public Health Order no. 485/09.05.2005, as amended, reunited on summons of the National Medicines Agency President in the ordinary meeting of 28.09.2007, in accord with Article 10 of Government Ordinance no. 125/1998 related to the set up, organisation and functioning of the National Medicines Agency, approved as amended through Law no. 594/2002, as further amended, agrees on the following

DECISION

Single article. – The Guideline on the issue and update procedure of Good Manufacturing Practice certificates is approved, according to the Annex which is integral part of this Decision.

PRESIDENT
of the Scientific Council
of the National Medicines Agency

Acad. Prof. Dr. Victor Voicu

ANNEX

Guideline on the issue and update procedure of Good Manufacturing practice (GMP) certificates

CHAPTER I
Scope

Art. 1. – (1) This Guideline is a translation into Romanian and an adaptation of the Guideline EMEA/INS/GMP/871/04 on the issue and update of the Good Manufacturing Practice (GMP) certificates, issued by the European Medicines Agency (EMEA).

CHAPTER II
Introduction

Art. 2. – Art. 823 (5) of Law 95/2006 on healthcare reform, Title XVII – The medicinal product, require a certificate of Good Manufacturing Practice to be issued to the manufacturer within 90 days of carrying out an inspection if the manufacturer complies with the principles and guidelines of GMP as provided for by Community law.

Art. 3. – (1) The GMP certificates issued, or the information indicating that a manufacturer does not comply, shall be entered into the EudraGMP Community database.

(2) The requirement specifically refers to inspections referred to in Art. 823 (1) of Directive 95/2006 and it includes therefore inspections of:

a) Manufacturers, importers and contract laboratories according to national and centrally organised inspection programmes;

b) Active substance manufacturers, in particular where there are grounds for suspecting noncompliance; these inspections are carried out in accordance with the NMA Scientific Council Decision No. 55/15.12.2006 on the approval of "Guidance on the occasions when it is appropriate for the NMA to conduct inspections at the premises of manufacturers of active substances used as starting materials"; this type of inspections includes requests by a manufacturer itself, member state, the European Commission or EMEA; it also includes requests by EDQM (European Directorate for the Quality of Medicines) on behalf of the European Commission or EMEA as part of the certification procedure for monographs of the European Pharmacopoeia;

c) Marketing authorisation holders in so far as compliance with Good Manufacturing Practice is concerned;

d) Manufacturers located in third countries.

(3) The requirement applies regardless as to whether the inspections are unannounced, routine or requested by a Member State, EC, EMEA, EDQM or manufacturer itself.

(4) In addition, where appropriate, and where the National Medicines Agency (NMA) chooses to do so, GMP certificates may be issued following inspection of manufacturers of investigational medicinal products for human use; in any case entry into EudraGMP database will be made to fulfil the requirements of Art. 66(1)f of Minister of Public Health Order No. 904/2006.

Art. 4. – This Guideline is intended to give interpretation on aspects of responsibilities of the issue, renewal and update of GMP certificates.

CHAPTER III

Use of certificates

Art. 5. – (1) GMP certificates are for the purpose of confirming to a manufacturer (whether for active substances or medicinal products) the overall conclusion of an inspection with respect to compliance with GMP.

(2) In some cases, particularly outside of the European Economic Area (EEA), they may be used by applicants to support the marketing authorisation dossier.

(3) Within the EEA, GMP certificates do not replace confirmation of the holding of a manufacturing authorisation.

Art. 6. – The GMP status of third country manufacturing sites for medicinal products and active substances may be confirmed using the EudraGMP database or, until this is fully operational, confirmed using the Community procedure for the exchange of information, transposed through the NMA Scientific Council Decision No. 15/2007.

Art. 7. – For active substances, the supporting document in regulatory submissions is the declaration by the Qualified Person of the manufacturing authorisation holder that uses the active substance as a starting material.

Art. 8. – GMP certificates issued by EEA authorities are recognised within the framework of the World Health Organisation (WHO) and within the Mutual Recognition Agreements (MRAs) were agreed.

CHAPTER IV

When GMP Certificates should be issued and enter the EudraGMP database Responsibility for issue of GMP Certificates

Art. 9. – For medicinal products, responsibility for issuing GMP certificates and placing entries into EudraGMP rests with the supervisory authority, including those certificates issued following inspections performed at the request of the EC, EMEA, EDQM, Member State or an active substance manufacturer as well as inspections performed by another Member State on behalf of the supervisory authority; if there is more than one supervisory authority for third country manufacturers then these authorities should agree on who will take on this responsibility but normally one of the supervisory authorities will lead the inspection and this one should take responsibility.

Art. 10. – In the case of an inspection of an active substance manufacturer, as the concept of supervisory authority does not apply, responsibility for the GMP certificate and EudraGMP entry rests with the authority that carries out or leads the inspection.

Art. 11. – Following each relevant inspection, a report in accordance with the Community format should be produced by the responsible inspector or inspection team, which should contain a clear statement as to whether or not the manufacturer complies with the principles and guidelines of GMP as provided for in Community legislation.

Art. 12. –Where this is the case, within 90 days of the last day of the inspection concerned, the supervisory authority should issue a GMP certificate in accordance with the Community format to the manufacturer that underwent the inspection; in the case of non-compliance see the relevant Community procedure.

Art. 13. – Each certificate should include a reference that enables traceability within the inspectorate that issued it so that the inspectorate can respond promptly to enquiries regarding authenticity.

Art. 14. –Duplicates of valid GMP certificates may be issued in response to a request from the manufacturer, or MRA partner authority in accordance with the terms of the agreement.

Circumstances where the issue of a GMP certificate to a manufacturer may not be applicable (other than in cases of failure to comply with GMP).

Art. 15. – If the aim of any particular visit to a site is not primarily to assess compliance with GMP and the issue of a certificate is therefore not foreseen, then this should be made clear to the concerned manufacturer at the outset.

Art. 16. – It may not be appropriate to issue a GMP certificate following an inspection in response to an application for, or variation to a manufacturing authorisation, even if the outcome of the inspection is positive with respect to the application, particularly where approval is based upon plans and commitments rather than a direct inspection of facilities and operations.

Art. 17. – (1) Normally, an inspection is conducted in a single visit over a consecutive period of days but it may be split into a number of separate visits.

(2) Provided the subsequent visits occur within a reasonable period of time of the first visit, as decided by national procedures, the individual visits may collectively be considered as one inspection for which a single certificate will be issued within 90 days of the last day of the last visit.

(3) The manufacturer should be informed of this beforehand.

Art. 18. – A GMP certificate is not issued to a third country manufacturer when the GMP status has been verified using the distant assessment procedure described in the Community procedure on co-coordinating the verification of the GMP status of manufacturers in third countries; a EudraGMP database entry is nevertheless made (see Art. 24 and 25).

Purpose of individual certificates

Art. 19. – (1) The certificate should include all operations deemed to be GMP compliant as a result of the inspection.

(2) For large sites in the EEA this may not necessarily include all authorised operations as several inspections may be needed to assess all the authorised operations over a period of time as agreed in Community procedures.

Art. 20. – Inspections performed at third country manufacturers are often particularly restricted in scope and provision is made for this in part 2 of the certificate format; for ease of database entry and to reduce the use of free text, the EudraGMP database contains standard phrases to cover the most common situations.

Responsibility for EudraGMP database entry

Art. 21. – The supervisory authority may enter the details of the certificate into the EudraGMP before or at the time the certificate itself is issued to the manufacturer, or as soon as possible thereafter; database entries will have a status of draft, current or withdrawn.

EudraGMP entry for GMP Certificates issued by MRA Partners

Art. 22. – (1) The information from GMP certificates issued by MRA partner authorities is, on the first occasion, input into EudraGMP by the requesting authority in the EEA.

(2) Once the necessary agreements are in place it is suggested that subsequent certificates for the same site are input directly by the MRA partner.

(3) In the absence of such an agreement subsequent certificates will continue to be input by the requesting authority in the EEA.

Distant assessment

Art. 23. – When the GMP status of a manufacturer located in a third country shall is verified using the distant assessment procedure described in the Community procedure on co-coordinating the verification of the GMP status of manufacturers in third countries, no certificate should be issued to the manufacturer in question but an entry in the EudraGMP database should nevertheless be made by the supervisory authority indicating in the relevant field that the distant assessment procedure was followed.

Investigational Medicinal Products for Human Use (IMPs)

Art. 24. – Law 95/2006 does not make reference to the issue of GMP certificates following an inspection of a manufacturer of IMPs, however the Member State may choose to do so.

Art. 25. –In order to facilitate the exchange of information on clinical trials, Art. 66 of Minister of Public Health Order No. 904/2006 requires a reference to inspections to be included in the European database and it has been agreed that the appropriate database is EudraGMP database for GMP inspections of manufacturers of IMPs; therefore, an entry should be made whether or not a certificate is issued to the manufacturer in question.

CHAPTER V
Non-compliance with GMP

Art. 26. – A separate Community procedure deals with the handling of non-compliance.

CHAPTER VI
Renewal and update of GMP Certificates

Art. 27. – (1) A certificate itself is not renewed, as it is a declaration of the status of GMP compliance at a particular point in time connected with a satisfactory inspection outcome.

(2) A new certificate will be issued following the next inspection, if appropriate.

(3) Entries in EudraGMP however require a different approach.

Art. 28. – (1) EudraGMP requires the Member State inputting new information to decide whether the new certificate replaces an existing entry for the site in question, in which case they must take action to withdraw the superseded information, or, whether the information is in addition to the existing information, in which case the information being supplemented should remain in the database.

(2) In the case of third country manufacturers with more than one supervisory authority it is possible that a different authority carries out the subsequent inspection but it is not possible for an authority to withdraw a database entry made by another authority; therefore both authorities have to work together to maintain the database in order that superseded information is withdrawn by the supervisory authority that originally input it.

Art. 29. – (1) However, sometimes it will be necessary to retain some of the existing information if it is not superseded following a new inspection.

(2) This would happen, for example, when the most recent inspection does not cover everything covered by the previous inspection; in this case the following action is appropriate:

a) Withdraw the existing certificate (or have the original issuing authority withdraw it) and re-issue it having removed the superseded information but retaining the original date of inspection.

b) Issue a new certificate with new information and the most recent inspection date.

Administrative updates and re-issue

Art. 30. – (1) An updated certificate may be issued to a manufacturer and input into EudraGMP by the authority that issued the last certificate at the manufacturer's request when administrative changes occur that affect the details appearing on the certificate and where the supervisory authority agrees that a re-inspection is not required; an example would be a change in the name of the manufacturer.

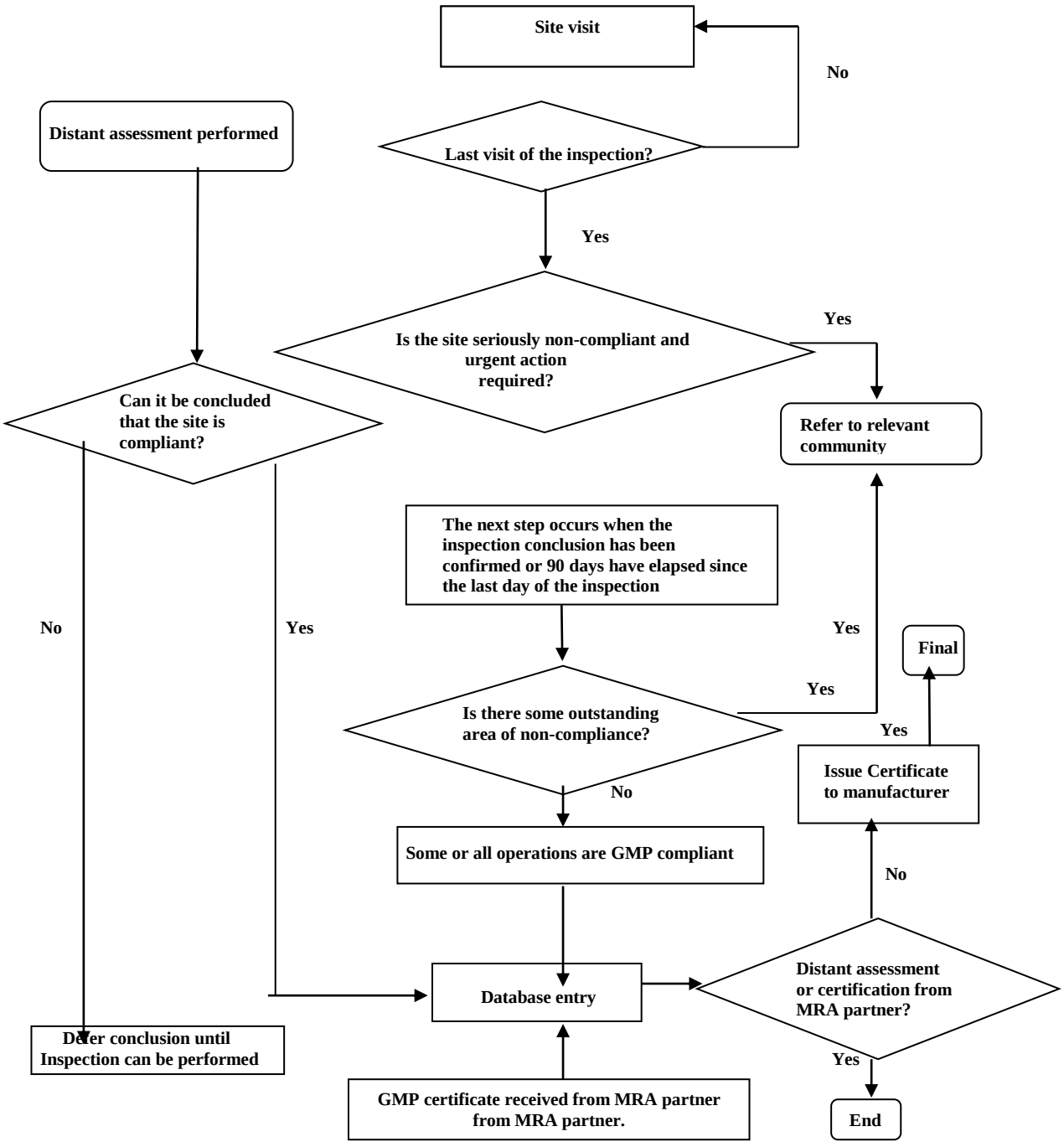
(2) These new certificates will supersede the existing certificate but will maintain the original date of inspection, since a new inspection will not have been carried out.

CHAPTER VII

Closure of a manufacturing site

Art. 31. – Member states should take all steps to ensure that when a site under its supervision ceases to operate, any GMP certificate is withdrawn from the Community database along with its manufacturing authorisation and noncompliance information.

ANNEX 1


Site visit
No
Distant assessment performed
Last visit of the inspection?
Yes
Is the site seriously non-compliant and urgent action required?
Yes
Can it be concluded that the site is compliant?
Refer to relevant community
The next step occurs when the inspection conclusion has been confirmed or 90 days have elapsed since the last day of the inspection
No
Yes
Yes
Final
Yes
Is there some outstanding area of non-compliance?
Yes
Issue Certificate to manufacturer
No
Some or all operations are GMP compliant
No
Database entry
Distant assessment or certification from MRA partner?
Defer conclusion until Inspection can be performed
Yes
GMP certificate received from MRA partner from MRA partner.
End