EUROPEAN COMMISSION
HEALTH AND FOOD SAFETY DIRECTORATE-GENERAL

Health systems, medical products and innovation
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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

The issue and update of GMP certificates

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Title	**The issue and update of GMP**
Date of adoption	May 2023
Date of entry into force	1 January 2024
Supersedes	Version adopted 21 September 2021
Reason for revision	Modifications were introduced as a result of the entry into application of Regulation (EU) 2019/6 on veterinary medicinal products and repealing Directive 2001/82/EC and Regulation (EU) 2019/5 amending Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.
Notes	GMP Certificates are issued, where appropriate, to manufacturers following an inspection in accordance with Art. 111(5) of Directive 2001/83/EC and 94 (1) of Regulation 2019/6. They are also entered into the Union database (EudraGMDP) as required in Arts 111(6) of Directive 2001/83/EC and 91 (3) of Regulation 2019/6.
Last publication date:	1 August 2024
Document version	1

The Issue and Update of GMP Certificates

1. Introduction

Art. 111 (5) of Directive 2001/83/EC and Art. 94 (1) of Regulation 2019/6as amended, 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 European Union law. The GMP certificates issued, or the information indicating that a manufacturer does not comply, shall be entered into the EudraGMDP database.

The requirement applies regardless as to whether the inspections are unannounced, routine or requested by a Member State, the European Commission, European Medicines Agency, EDQM or manufacturer itself.

This document is intended to give interpretation on aspects of responsibilities of the issue, renewal and update of GMP certificates.

2. Use of Certificates

GMP certificates are for the purpose of confirming the overall conclusion of an inspection with respect to compliance with GMP. In some cases, normally for sites outside of the EEA, they may be used by applicants to support regulatory submissions. Within the EEA they do not replace confirmation of the holding of a manufacturing authorisation. GMP certificates may be verified using the EudraGMDP database.

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.

GMP certificates issued by EEA authorities are recognised within the framework of WHO and to fulfil obligations under the Mutual Recognition Agreements.

3. When GMP Certificates should be issued and EudraGMDP entry

3.1 Responsibility for issue of GMP Certificates

For medicinal products responsibility for issuing GMP certificates and placing entries into EudraGMDP rests with the supervisory authority, including those certificates issued following inspections performed at the request of the Commission, EMA, EDQM, Member State or an active substance manufacturer. If more than one authority carries out an inspection of a third country manufacturer then these authorities should agree on who will take on this responsibility for issuing the certificate.

Following each relevant inspection, a report in accordance with the Union 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 European Union legislation. Where this is the case, within 90 days of the last day of the inspection concerned, the authority should issue a GMP certificate in accordance with the Union format to the manufacturer that underwent the inspection. In the case of non-compliance see the relevant Union procedure.

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.

Hard copy 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, but all parties should be encouraged to use EudraGMDP wherever possible

3.2 Circumstances where the issue of a certificate to a manufacturer may not be applicable (other than in cases of failure to comply with GMP) are as follows:

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.

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.

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. Provided the subsequent visits occur within a short period of time after the first visit 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. The manufacturer should be informed of this beforehand.

Depending on national legislation, paper GMP certificates need not be issued to manufacturers of investigational medicinal products. Nevertheless EudraGMDP entry is required (see section 3.7).

3.3 Scope of individual certificates

The certificate should include all operations deemed to be GMP compliant as a result of the inspection. 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 Union procedures.

Inspections may be 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 EudraGMDP database contains a drop down menu but the certificate should include free text sufficiently explaining the reasons for the restriction. See also section 4.

3.4 Responsibility for EudraGMDP database entry

The authority performing the inspection is responsible for entering the details of the certificate into EudraGMDP within 90 days of the relevant inspection.

3.5 EudraGMDP entry for GMP Certificates issued by MRA Partners

MRA partners are encouraged to use GMP Certificates uploaded into EudraGMDP by EEA authorities rather than request paper versions. Similarly, they are authorised to upload certificates themselves upon the request of EEA authorities or local manufacturer for the purposes of the MRAs.

3.6 Investigational Medicinal Products for Human Use (IMPs)

Directive 2001/83/EC or Regulation 536/2004 do not make reference to the issue of GMP certificates following an inspection of a manufacturer of IMPs, however Member States may choose to do so, in order to facilitate the exchange of information on clinical trials. It has been agreed that the appropriate database is EudraGMDP database for GMP inspections of manufacturers of IMPs.

3.7 Investigational Medicinal Products for Veterinary Use (VIMPs)

Regulation 2019/06 does not make reference to the issue of GMP certificates following an inspection of a manufacturer of veterinary IMPs, however Member States may choose to do so,

in order to facilitate the exchange of information on clinical trials. It has been agreed that the appropriate database is EudraGMDP database for GMP inspections of manufacturers of IMPs.

4. Non-compliance with GMP

A separate Union procedure deals with the handling of non-compliance.

5. Renewal and update of GMP Certificates[1]

5.1 A certificate itself is not normally renewed, as it is a declaration of the status of GMP compliance at a particular point in time connected with a satisfactory inspection outcome. A new certificate will be issued following the next inspection, if appropriate. Entries in EudraGMDP however require a different approach.

EudraGMDP 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.

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 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.

It may not always be appropriate to withdraw existing information that is not superseded following a new inspection. 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:

- 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.
- Issue a further new certificate with new information and the most recent inspection date.

5.2 Administrative updates and re-issue

An updated certificate may be issued to a manufacturer and input into EudraGMDP by the authority that issued the last certificate at the request of a manufacturer 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. These new certificates will supersede the existing certificate but will maintain the original date of inspection, as an inspection will not have been carried out.

5.3 GMP certificate validity periods

5.3.1 Initial validity period

A GMP certificate reflects the status of the manufacturing site at the time of the inspection. It should not be relied upon to reflect the compliance status if more than three years have elapsed since the date of that inspection, unless extended by the issuing authority.
On the basis of inspection outcome and risk evaluation, the issuing authority may condition a GMP certificate to give a specific validity of less than three years by an entry in the Restrictions or Clarifying remarks field. In this case, the validity period may not be extended. A re-inspection may (with the exception of active substances, where permitted by the national competent authority) be performed by the issuing authority within the required timeframe indicated by the restriction.

5.3.2 Extension of GMP certificate validity period

GMP certificates may continue to be used for the period extended by the issuing authority. They may not be used to support regulatory applications beyond the stated validity period.
A GMP certificate which was not initially restricted in respect of validity period may be extended if a re-inspection is not performed within the three year timeframe. The extension of validity may be up to a maximum of:

- a further two years for manufacturers located in the EEA and for manufacturers located in Third Countries (i.e. total of five years from date of inspection)

Extensions of GMPc validity period should not lead to changes in the scope (buildings, lines or manufacturing activity) of the certificate.
The decision to extend the validity period should be based on a GMP compliance risk assessment of relevant factors by the issuing authority. This may include, but not be limited to, those requirements listed in the Annex to the "Outline of a Procedure for Coordinating the verification of the GMP status of Manufacturers in Third Countries" SOP.

GMP certificates should be extended by issuing a new certificate with reference to the previous inspection date. This provides traceability to previous versions.
An extended certificate must include a conditioning remark on the GMP certificate and, for sites located in a third country, an update to the EudraGMDP inspection planning module, to indicate the next scheduled inspection date and scope.

- The following conditioning text should be used in the Restrictions or Clarifying remarks field of the GMP certificate:

"Following a risk-based review of GMP compliance information conducted on [date of review], the validity period of this certificate is extended to [new date of expiry].

- GMP certificates extended for third country manufacturers should **also** include the following text:

  "National Competent Authorities may view future inspection scheduling in the EudraGMDP planning module"

5.3.3 Change in EU supervisory authority of a third country manufacturer when extending GMP certificate validity period

A third country manufacturer may change its supervisory authority (SA) between inspections. In this case, if GMP certificate extension is required before re-inspection by the new SA, both authorities have shared responsibilities.
The desktop compliance review and decision to extend the GMP certificate validity period must be performed by the SA that issued the original certificate.
The new SA is responsible for entering information in EudraGMDP planning module and performing the next inspection.
Communication between both authorities is important to ensure re-inspection scheduling which is compatible with the compliance assessment and extension of certificate validity.

5.3.4 Validity period of GMP certificates or compliance documents following remote review of information

If a GMP certificate (or equivalent document(s)) has been issued by a SA following a review of compliance information from trusted regulatory partners or 'distant assessment' procedure, it should not be extended beyond three years. A new (full) assessment or inspection should be performed.

6. Closure of manufacturing site

Member states should take steps to ensure that when a site under its supervision ceases to operate, any GMP certificate is withdrawn from the EudraGMDP database along with any manufacturing authorisation and non-compliance information.