



Brussels, 12 October 2015

EudraLex

Volume 4

EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use

Annex 16: Certification by a Qualified Person and Batch Release

Legal basis for publishing the detailed guidelines: Article 47 of Directive 2001/83/EC, as amended, on the Community code relating to medicinal products for human use and Article 51 of Directive 2001/82/EC on the Community code relating to veterinary medicinal products. This document provides guidance for the interpretation of the principles and guidelines of good manufacturing practice (GMP) for medicinal products as laid down in Directive 2003/94/EC for medicinal products for human use and Directive 91/412/EEC for veterinary use.

Status of the document: Revision.

Reasons for changes: The Annex has been revised to reflect the globalisation of the pharmaceutical supply chains and the introduction of new quality control strategies. The revision has been carried out in the light of Directive 2011/62/EU amending Directive 2001/83/EC as regards the prevention of the entry into the legal supply chain of falsified medicinal products. This version also implements ICH Q8, Q9 and Q10 documents, and interpretation documents, such as the manufacturing and importation authorisation (MIA) interpretation document, as applicable. Also, some areas, where the interpretation by Member States has not been consistent, have been clarified.

Deadline for coming into operation: 15 April 2016.

Scope

This Annex provides guidance on the certification by a Qualified Person (QP) and on batch release within the European Union (EU) of medicinal products for human or veterinary use holding a marketing authorisation (MA) or made for export. The principles of this guidance also apply to investigational medicinal products (IMP) for human use, subject to any difference in the legal provisions and more specific guidance published by the European Commission.

The relevant legislative requirements are provided in Article 51 of Directive 2001/83/EC, as amended, and in Article 55 of Directive 2001/82/EC. Notice is taken of the arrangements referred to in Article 51(2) of Directive 2001/83/EC, as amended, and Article 55(2) of Directive 2001/82/EC, e.g. Mutual Recognition Agreements (MRA).

This Annex does not address the “Official Control Authority Batch Release” which may be specified for certain blood and immunological products in accordance with Articles 109, 110, 113 and 114 of Directive 2001/83/EC, as amended, and Articles 81 and 82 of Directive 2001/82/EC. However, this Annex does apply to the QP certification and subsequent release of such batches.

The basic arrangements for batch release for a product are defined by its MA. Nothing in this Annex should be taken as overriding those arrangements.

General principles

The ultimate responsibility for the performance of a medicinal product over its lifetime, its safety, quality and efficacy, lies with the marketing authorisation holder (MAH).

However, the QP is responsible for ensuring that each individual batch has been manufactured and checked in compliance with laws in force in the Member State where certification takes place, in accordance with the requirements of the marketing authorisation (MA) and with Good Manufacturing Practice (GMP).

The process of batch release comprises of:

- i. The checking of the manufacture and testing of the batch in accordance with defined release procedures.
- ii. The certification of the finished product batch performed by a QP signifying that the batch is in compliance with GMP and the requirements of its MA. This represents the quality release of the batch.
- iii. The transfer to saleable stock, and/or export of the finished batch of product which should take into account the certification performed by the QP. If this transfer is performed at a site other than that where certification takes place, then the arrangement should be documented in a written agreement between the sites.

The purpose of controlling batch release is notably to ensure that:

- i. The batch has been manufactured and checked in accordance with the requirements of its MA.
- ii. The batch has been manufactured and checked in accordance with the principles and guidelines of GMP.
- iii. Any other relevant legal requirements are taken into account.
- iv. In the event that a quality defect as referred to in Chapter 8 of EudraLex, Volume 4, Part I, needs to be investigated or a batch recalled, to ensure that any QPs

involved in the certification or confirmation¹ and any relevant records are readily identifiable.

1. THE PROCESS OF CERTIFICATION

- 1.1. Each batch of finished product must be certified² by a QP within the EU before being released for sale or supply in the EU or for export. Certification can only be performed by a QP of the manufacturer and/or importer which are described in the MA.
- 1.2. Any QP involved in the certification, or confirmation of a batch must have detailed knowledge of the steps for which they are taking responsibility. The QPs should be able to prove their continuous training regarding the product type, production processes, technical advances and changes to GMP.
- 1.3. There may be several sites involved in the various stages of manufacture, importation, testing and storage of a batch before it undergoes certification. Regardless of how many sites are involved, the QP performing certification of the finished product must ensure that all necessary steps have been completed under accepted pharmaceutical quality systems to assure compliance of the batch with GMP, the MA and any other legal obligations in the Member State where certification is taking place.
- 1.4. For manufacturing steps performed at sites in the EU each manufacturing site must have at least one QP.
 - 1.4.1 Where the site only undertakes partial manufacturing operations in relation to a batch, then a QP at that site must at least confirm that the operations undertaken by the site have been performed in accordance with GMP and the terms of the written agreement detailing the operations for which the site is responsible. If the QP is responsible for providing confirmation of compliance for those operations with the relevant MA, then the QP should have access to the necessary details of the MA.
 - 1.4.2 The QP who performs certification of the finished product batch may assume full responsibility for all stages of manufacture of the batch or this responsibility may be shared with other QPs who have provided confirmation for specified steps in the manufacture and control of a batch. These could be other QPs who are operating under the same manufacturing authorisation (MIA) holder or QPs operating under different MIA holders.
 - 1.4.3 Any sharing of responsibilities amongst QPs in relation to compliance of a batch must be defined in a document formally agreed by all parties. This document should detail responsibility for assessment of the impact any deviation(s) has/have on compliance of the batch with GMP and the MA.
- 1.5. For medicinal products manufactured outside the EU, physical importation and certification are the final stages of manufacturing which precede the transfer to saleable stock of the batch.
 - 1.5.1 The process of certification as described in Section 1 of this Annex, applies to all medicinal products intended to be released for the EU markets, or for export, irrespective of the complexity of the supply chain and the global locations of manufacturing sites involved.

¹ Information required for the confirmation, where QP responsibilities for the batch are being transferred between sites, is presented in Appendix I to this Annex.

² The contents of a batch certificate for medicinal products are presented in Appendix II to this Annex.

- 1.5.2 In accordance with the principles described in Section 1.4 of this Annex, the QP certifying the finished medicinal product batch may take account of the confirmation by, and share defined responsibilities with, other QPs in relation to any manufacturing or importation operations taking place at other sites in the EU and other manufacturing authorisation holders defined in the relevant MA.
- 1.5.3 Conditions of storage and transport for the batch and the sample, if sent separately, should be taken into account by the QP before certification of a batch.
- 1.5.4 The QP certifying the finished product is responsible for ensuring that each finished medicinal product batch has been manufactured in accordance with GMP and the MA. Unless an MRA or similar agreement is in place between the EU and the exporting country, the QP is also responsible for ensuring that the finished medicinal product batch has undergone in a Member State a full qualitative analysis, a quantitative analysis of at least all the active substances and all the other tests or checks necessary to ensure the quality of medicinal products is in accordance with the requirements of the MA.
- 1.5.5 Sampling of imported product should be fully representative of the batch. Samples may either be taken after arrival in the EU, or be taken at the manufacturing site in the third country in accordance with a technically justified approach which is documented within the company's quality system. Responsibilities in relation to the sampling should be defined in a written agreement between the sites. Any samples taken outside the EU should be shipped under equivalent transport conditions as the batch that they represent.
- 1.5.6 Where sampling is performed at a third country manufacturing site, the technical justification should include a formal Quality Risk Management process to identify and manage any risks associated with this approach. This should be fully documented and include at least the following elements:
- i. Audit of the manufacturing activity including any sampling activity at the third country site and evaluation of subsequent transportation steps of both the batch and samples to ensure that the samples are representative of the imported batch.
 - ii. A comprehensive scientific study, including data to support any conclusions that samples taken in the third country are representative of the batch after importation. This study should at least include:
 - Description of the sampling process in the third country.
 - Description of the transported conditions of the sample and the imported batch. Any differences should be justified.
 - Comparative analysis of samples taken in the third country and samples taken after importation.
 - Consideration of the time interval between sampling and importation of the batch and generation of data to support appropriate defined limits.
 - iii. Provision for random periodic analysis of samples taken after importation to justify ongoing reliance on samples taken in a third country.

- iv. A review of any unexpected result or confirmed out of specification result. These may have implications for reliance on sampling performed at the third country manufacturing site and should be notified to the Supervisory Authority for the site where certification is performed. Such an occurrence should be regarded as a potential quality defect and investigated in line with the guidance in Chapter 8 of EudraLex, Volume 4, Part I.
- 1.5.7 Different imported finished product batches may originate from the same bulk product batch. The QPs certifying the different finished product batches may base their decision on the quality control testing of the first imported finished batch provided that a justification has been documented based on Quality Risk Management principles. This should take into account the provisions of paragraph 1.5.6 in relation to reliance on any samples taken in third countries. Evidence should be available to ensure that the integrity and identity of the imported finished product batch has been established through documented verification of at least the following:
- i. Relevant requirements for storage of the bulk product prior to packaging have been satisfied;
 - ii. The finished product batch has been stored and transported under the required conditions;
 - iii. The consignment has remained secure and there is no evidence of tampering during storage or transportation;
 - iv. Correct identification of the product has been established;
 - v. The sample(s) tested are representative of all finished product batches derived from the bulk batch.
- 1.6 The QP must personally ensure that the following operational responsibilities are fulfilled prior to certification of a batch for release to market or for export:
- i. Certification is permitted under the terms of the MIA.
 - ii. Any additional duties and requirements of national legislation are complied with.
 - iii. Certification is recorded in a register or equivalent document.
- 1.7 In addition, the QP has responsibility for ensuring points 1.7.1 to 1.7.21 are secured. These tasks may be delegated to appropriately trained personnel or third parties. It is recognised that the QP will need to rely on the pharmaceutical quality system and the QP should have on-going assurance that this reliance is well founded.
- 1.7.1 All activities associated with manufacture and testing of the medicinal product have been conducted in accordance with the principles and guidelines of GMP.
- 1.7.2 The entire supply chain of the active substance and medicinal product up to the stage of certification is documented and available for the QP. This should include the manufacturing sites of the starting materials and packaging materials for the medicinal product and any other materials deemed critical through a risk assessment of the manufacturing process. The document should preferably be in the format of a comprehensive diagram, where each party, including subcontractors of critical steps such as the sterilisation of components and equipment for aseptic processing, are included.

- 1.7.3 All audits of sites involved in the manufacture and the testing of the medicinal products and in the manufacture of the active substance have been carried out and that the audit reports are available to the QP performing the certification.
- 1.7.4 All sites of manufacture, analysis and certification are compliant with the terms of the MA for the intended territory.
- 1.7.5 All manufacturing activities and testing activities are consistent with those described in the MA.
- 1.7.6 The source and specifications of starting materials and packaging materials used in the batch are compliant with the MA. Supplier quality management systems are in place that ensure only materials of the required quality have been supplied.
- 1.7.7 For medicinal products that fall within the scope of Directive 2001/83/EC, as amended, or Directive 2001/82/EC, the active substances have been manufactured in accordance with GMP and, where required, distributed in accordance with Good Distribution Practice (GDP) for Active Substances.
- 1.7.8 The importation of active substances used in the manufacture of medicinal products for human use should comply with the requirements of Article 46(b) of Directive 2001/83/EC, as amended.
- 1.7.9 For medicinal products that fall within the scope of Directive 2001/83/EC, as amended, the excipients have been manufactured in accordance with the ascertained GMP referred to in Article 46 (f) of that Directive.
- 1.7.10 When relevant, the TSE (Transmissible Spongiform Encephalopathy) status of all materials used in batch manufacture is compliant with the terms of the MA.
- 1.7.11 All records are complete and endorsed by appropriate personnel. All required in-process controls and checks have been made.
- 1.7.12 All manufacturing and testing processes remain in the validated state. Personnel are trained and qualified as appropriate.
- 1.7.13 Finished product quality control (QC) test data complies with the Finished Product Specification described in the MA, or where authorised, the Real Time Release Testing programme.
- 1.7.14 Any regulatory post-marketing commitments relating to manufacture or testing of the product have been addressed. On-going stability data continues to support certification.
- 1.7.15 The impact of any change to product manufacturing or testing has been evaluated and any additional checks and tests are complete.
- 1.7.16 All investigations pertaining to the batch being certified (including out of specification and out of trend investigations) have been completed to a sufficient level to support certification.
- 1.7.17 Any on-going complaints, investigations or recalls do not negate the conditions for certification of the batch in question.
- 1.7.18 The required technical agreements are in place.
- 1.7.19 The self-inspection programme is active and current.
- 1.7.20 The appropriate arrangements for distribution and shipment are in place.

- 1.7.21 In the case of medicinal products for human use intended to be placed on the market in the Union, the safety features referred to in Article 54(o) of Directive 2001/83/EC, as amended, have been affixed to the packaging, where appropriate.
- 1.8 For certain products, special guidance may apply, such as EudraLex, Volume 4, Annex 2: Manufacture of Biological active substances and Medicinal Products for Human Use, and Annex 3: Manufacture of Radiopharmaceuticals.
- 1.9 In the case of parallel importation and parallel distribution any repackaging operation carried out on a batch which has already been released must be approved by the competent authority of the intended market.
- 1.9.1 Prior to certification of a repacked batch the QP should confirm compliance with national requirements for parallel importation and EU rules for parallel distribution.
- 1.9.2 The QP of the MIA holder, who is named responsible for the certification of the batch in the MA of the repackaged finished product, certifies that the repackaging has been performed in accordance with the relevant authorisation pertaining to the repackaged product and GMP.
- 1.10 Recording of QP certification.
- 1.10.1 The certification of a medicinal product is recorded by the QP in a register or equivalent document provided for that purpose. The record should show that each production batch satisfies the provisions of Article 51 of Directive 2001/83/EC, as amended, or Article 55 of Directive 2001/82/EC. The record must be kept up to date as operations are carried out and must remain at the disposal of the agents of the competent authority for the period specified in the provisions of the Member State concerned and in any event for at least five years.
- 1.10.2 The control report referred to in Article 51 of Directive 2001/83/EC, as amended, or Article 55 of Directive 2001/82/EC or another proof for release to the market in question, based on an equivalent system, should be made available for the batch in order to be exempted from further controls when entering another Member State.

2. RELYING ON GMP ASSESSMENTS BY THIRD PARTIES, E.G. AUDITS

In some cases the QP will rely on the correct functioning of the pharmaceutical quality system of sites involved in the manufacture of the product and this may be derived from audits conducted by third parties.

- 2.1 Relying on assessment by third parties, e.g. audits, should be in accordance with Chapter 7 of the GMP Guide in order to appropriately define, agree and control any outsourced activity.
- 2.2 Special focus should be given to the approval of audit reports:
- i. The audit report should address general GMP requirements, as for example the quality management system, all relevant production and quality control procedures related to the supplied product, e.g. active substance manufacturing, quality control testing, primary packaging, etc. All audited areas should be accurately described resulting in a detailed report of the audit.
 - ii. It should be determined whether the manufacture and quality control of the active substance and medicinal product complies with GMP, or in case

of manufacture in third countries, GMP at least equivalent to that referred to in Article 46 of Directive 2001/83/EC, as amended, or Article 50 of Directive 2001/82/EC.

- iii. In case of outsourced activities compliance with the MA should be verified.
- iv. The QP should ensure that a written final assessment and approval of third party audit reports have been made. The QP should have access to all documentation which facilitates review of the audit outcome and continued reliance on the outsourced activity.
- v. Outsourced activities with critical impact on product quality should be defined in accordance with the principles of Quality Risk Management as described in Part III of EudraLex, Volume 4. According to this, the QP should be aware of the outcome of an audit with critical impact on the product quality before certifying the relevant batches.
- vi. Repeated audits should be performed in accordance with the principles of Quality Risk Management.

3. HANDLING OF UNEXPECTED DEVIATIONS

Provided registered specifications for active substances, excipients, packaging materials and medicinal products are met, a QP may consider confirming compliance or certifying a batch where an unexpected deviation concerning the manufacturing process and/or the analytical control methods from details contained within the MA and/or GMP has occurred. The deviation should be thoroughly investigated and the root cause corrected. This may require the submission of a variation to the MA for the continued manufacture of the product.

- 3.1 The impact of the deviation should be assessed in accordance with a quality risk management process using an appropriate approach such as described in Part III of the GMP Guide. The quality risk management process should include the following;
 - i. Evaluation of the potential impact of the deviation on quality, safety or efficacy of the batch(es) concerned and conclusion that the impact is negligible.
 - ii. Consideration of the need to include the affected batch(es) in the ongoing stability programme.
 - iii. In the case of biological medicinal products, consideration that any deviations from the approved process can have an unexpected impact on safety and efficacy.

Taking account that responsibilities may be shared between more than one QPs involved in the manufacture and control of a batch, the QP performing certification of a batch of medicinal product should be aware of and take into consideration any deviations which have the potential to impact compliance with GMP and/or compliance with the MA.

4. THE RELEASE OF A BATCH

- 4.1 Batches of medicinal products should only be released for sale or supply to the market after certification by a QP as described above. Until a batch is certified, it should remain at the site of manufacture or be shipped under quarantine to another site which has been approved for that purpose by the relevant Competent Authority.

- 4.2 Safeguards to ensure that uncertified batches are not transferred to saleable stock should be in place and may be physical in nature, e.g. the use of segregation and labelling or electronic in nature, e.g. the use of validated computerised systems. When uncertified batches are moved from one authorised site to another, the safeguards to prevent premature release should remain.
- 4.3 The steps necessary to notify QP certification to the site where the transfer to saleable stock is to take place should be defined within a technical agreement. Such notification by a QP to the site should be formal and unambiguous and should be subject to the requirements of Chapter 4 of EudraLex, Volume 4, Part I.

5. GLOSSARY

Certain words and phrases in this annex are used with the particular meanings defined below. Reference should also be made to the Glossary in the main part of the Guide.

Certification of the finished product batch. The certification in a register or equivalent document by a QP, as defined in Article 51 of Directive 2001/83/EC, as amended, and Article 55 of Directive 2001/82/EC, and represents the quality release of the batch before the batch is released for sale or distribution.

Confirmation (Confirm and confirmed have equivalent meanings). A signed statement by a QP that a process or test has been conducted in accordance with GMP and the relevant marketing authorisation or clinical trial authorisation, product specification file and/or technical agreement, as applicable, as agreed in writing with the QP responsible for certifying the finished product batch before release. The QP providing a confirmation takes responsibility for those activities being confirmed.

Finished product batch. With reference to the control or test of the finished product, a finished medicinal product batch is described in Annex I, Part I, point 3.2.2.5, of Directive 2001/83/EC and Annex I, Part 2, section E, of Directive 2001/82/EC. In the context of this annex the term in particular denotes the batch of product in its final pack for release to the market.

Importer. The holder of the authorisation required by Article 40(3) of Directive 2001/83/EC, as amended, and Article 44(3) of Directive 2001/82/EC for importing medicinal products from third countries.

Qualified Person (QP). The person defined in Article 48 of Directive 2001/83/EC, as amended, and Article 52 of Directive 2001/82/EC.

Appendix I

Content of the confirmation of the partial manufacturing of a medicinal product

[LETTER HEAD OF MANUFACTURER WHO CARRIED OUT THE MANUFACTURING ACTIVITY]

1. Name of the product and description of the manufacturing stage (e.g. paracetamol 500 mg tablets, primary packaging into blister packs).
2. Batch number.
3. Name and address of the site carrying out the partial manufacturing.
4. Reference to the Technical Quality Agreement (in accordance with Chapter 7 of the Guide).
5. Confirmation statement.

I hereby confirm that the manufacturing stages referred to in the Technical Quality Agreement have been carried out in full compliance with the GMP requirements of the EU and the terms described in the Agreement for ensuring compliance with the requirements of the Marketing Authorisation(s) as provided by [Contract Giver/manufacturer certifying and releasing the batch].

6. Name of the Qualified Person confirming the partial manufacturing.
7. Signature of Qualified Person confirming the partial manufacturing.
8. Date of signature.

Appendix II

Content of the Batch Certificate for Medicinal Products

[LETTER HEAD OF THE BATCH CERTIFYING AND RELEASING MANUFACTURER]

1. Name, strength/potency, dosage form and package size (identical to the text on the finished product package).
2. Batch number of the finished product.
3. Name of the destination country/countries of the batch, at least when within the EU.
4. Certification statement.

I hereby certify that all the manufacturing stages of this batch of finished product have been carried out in full compliance with the GMP requirements of the EU and [when within the EU] with the requirements of the Marketing Authorisation(s) of the destination country/countries.

5. Name of the Qualified Person certifying the batch.
6. Signature of the Qualified Person certifying the batch.
7. Date of signature.