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Annex 16

Certification by a Qualified Person and Batch Release

Legal basis for publishing the detailed guidelines:

Article 47 of Directive 2001/83/EC 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 1

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, and to implement ICH Q8, Q9 and Q10 documents, and interpretation documents, such as the 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: <6 months from publication>

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Certification by a Qualified Person and Batch Release

1. Scope

1.1. This Annex provides guidance on the certification by a Qualified Person (QP) and on batch release within the European Economic Area (EEA) of medicinal products for human or veterinary use holding a marketing authorisation or made for export. The principles of this guidance also apply to investigational medicinal products, subject to any difference in the legal provisions and more specific guidance in Annex 13 to the Guide.

1.2. The relevant legislative requirements are contained in Article 51 of Directive 2001/83/EC, in Article 55 of Directive 2001/82/EC and in Article 13.3 of Directive 2001/20/EC. Notice is taken of the arrangements referred to in Article 51(2) of Directive 2001/83/EC and Article 55(2) of Directive 2001/82/EC (e.g. Mutual Recognition Agreements MRA).

1.3. 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, and Articles 81 and 82 of Directive 2001/82/EC.

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

2. General principles

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

2.2. However, the responsibility for ensuring that a particular batch has been manufactured in accordance with its marketing authorisation, with EU Good Manufacturing Practice (GMP), or equivalent, and that it is in compliance with the laws in force in the Member State where certification takes place and of the destination country of the medicinal product, lies with the QP certifying that batch as being suitable for release.

2.3. The process of batch release comprises of:

2.3.1 The checking of the manufacture and testing of the batch in accordance with defined release procedures.

2.3.2 The certification of the finished product batch performed by a Qualified Person signifying that the batch is in compliance with EU GMP and the requirements of its marketing authorisation (MA).

2.3.3 Assigning of release status to the finished batch of product which takes into account the certification performed by the QP. This is the final step in the process which effectively releases the batch for sale or export. This could be done by the QP as an integral part of certification or it could be done afterwards by another person. In this case, this arrangement should be delegated by the QP in a SOP or contract.

2.4. The purpose of controlling batch release is notably to ensure that

2.4.1 The batch has been manufactured and checked in accordance with the requirements of its marketing authorisation;

2.4.2 The batch has been manufactured and checked in accordance with the principles and guidelines of EU Good Manufacturing Practice, or equivalent;

2.4.3 Any other relevant legal requirements, e.g. of the destination country, are taken into account;

2.4.4 In the event that a defect needs to be investigated or a batch recalled, to ensure that the QP, who certified the batch, and the relevant records are readily identifiable.

3. The process of certification

3.1. Each batch of finished product must be certified by a QP within the EEA before being released for sale or supply in the EEA or for export.

Certification can only be performed by a QP of a Manufacturing and Importation Authorisation (MIA) holder named in the MA.

3.2. 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 demonstrate knowledge of the product type, production processes, technical advances and changes to GMP.

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 through an agreed quality management system to assure compliance of the batch with GMP, the Marketing Authorisation, and any other legal obligations in the member state where certification is taking place or in the destination country.

3.3. Manufacturing steps performed at sites in the EEA

Each manufacturing site in the EEA must have at least one QP.

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 confirming compliance of those operations with the relevant marketing authorisation then it is expected that the QP has access to the necessary details of the Marketing Authorisation to facilitate declaration of compliance.

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 confirmed compliance of specified steps in the manufacture and control of a batch. These could be other QPs who are operating under the same manufacturing authorisation holder or QPs operating under different manufacturing authorisation holders.

Any division of responsibilities amongst QPs in relation to compliance of the finished batch with GMP, the marketing authorisation and any other legal requirement must be defined;

i) in a written agreement between the sites where the QPs are located at different manufacturing authorisation holders.

ii) in a procedure where the QPs are operating at a single manufacturing authorisation holder.

The written agreement and procedure should include details on the responsibility for assessment of the impact of any deviations on compliance of the batch with GMP and the Marketing Authorisation.

A template for the confirmation is presented as an Attachment.

3.4. Manufacturing site(s) outside the EEA

For medicinal products manufactured outside the EEA, physical importation, certification and batch release are the final stages of manufacturing.

3.4.1 The process of certification as described in Section 3 of this Annex, applies to all medicinal products intended to be released for the EEA markets, or for export, irrespective of the complexity of the supply chain and the global locations of manufacturing sites involved.

3.4.2 Importation activities including at least receiving, sampling, storage of the un-released and un-certified batch, quality control testing, certification and release should be conducted by authorised sites in the EEA according to the requirements of Directive 2001/83/EC, Directive 2001/82/EC and Directive 2001/20/EC.

3.4.3 In accordance with the principles described in Section 3.3 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 sites in the EEA where this other manufacturing authorisation holder is defined in the relevant marketing authorisation.

3.4.4 Conditions of storage and transport should be taken into account by the QP during certification of a batch.

3.4.5 The QP certifying the finished product is responsible for ensuring that each finished medicinal production batch has been manufactured in accordance with GMP and the MA. Also, unless an MRA or similar agreement is in place between the EEA and the exporting country, that it 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, or in accordance with an approved Real Time Release Testing programme to ensure the quality of medicinal products in accordance with the requirements of the marketing authorisation.

3.4.6 Sampling of imported product should in full be representative of the batch and, therefore, be taken after arrival in the EEA

3.4.7 Where there is a risk that any sample would not appropriately represent the batch (e.g. sample for sterility test of an aseptically filled batch), it may be necessary to take additional samples during processing in the third country. Such an approach should be

technically justified. These samples should be shipped with and under the same conditions as the batch they represent. If sent separately it should be demonstrated that the samples are still representative of the imported batch.

3.4.8 When different finished product batches originating from the same bulk product batch are imported, the QPs certifying the different finished product batches may base their decision on the quality control testing of another imported finished batch originating from the same bulk product batch provided that the ID and assay testing are conducted on each occasion within the EEA and there is secured documented evidence that :

- The finished product batch originates from the same bulk product batch
- The finished products have been stored and transported in similar conditions
- The bulk product has been stored in similar conditions before completed packaging,
- The samples tested are representative of the whole batch.

3.5. Operational responsibilities of the QP prior to certification of a batch for release to market or for export, the QP must personally ensure that:

3.5.1 Certification is permitted under the terms of the manufacturing/importation authorisation (MIA).

3.5.2 Any additional duties and requirements of national legislation are complied with.

3.5.3 Certification is recorded in a register or equivalent document.

In addition the QP has responsibility for ensuring the following points 3.5.4 – 3.5.22. These may be delegated to appropriately trained personnel or third parties. It is recognised that the QP will need to rely on a quality management system. The QP should have on-going assurance that this reliance is well founded.

3.5.4 All activities associated with manufacture and testing of the medicinal product have been conducted in accordance with the principles and guidelines of EU GMP.

3.5.5 The entire supply chain of the medicinal product, starting from the manufacturing sites of the starting materials and components, and including all parties involved in any manufacturing and importation activities of the medicinal product, is documented and available for the QP. The document should preferably be in the format of a comprehensive diagram, where each party, including subcontractors of critical steps such as e.g. the sterilisation of components and equipment for aseptic processing, are included.

3.5.6 All sites of manufacture, analysis and certification are compliant with the terms of the marketing authorisation (MA) for the intended territory.

3.5.7 All manufacturing activities and testing activities are consistent with those registered in the marketing authorisation

3.5.8 The source and specifications of starting materials and packaging materials used in the batch are compliant with the MA. A supplier quality management system is in place which ensures that only materials of the required quality have been supplied

3.5.9 The active substances used in the manufacturing of the finished products have been manufactured in accordance with GMP and, where required, imported and distributed in accordance with Good Distribution Practices (GDP). When imported, and as relevant, the requirements of Article 46b of Directive 2001/83/EC are met.

3.5.10 The excipients used in the manufacturing of the finished product have been manufactured, as relevant, in accordance with the ascertained manufacturing practice referred to in Article 46 (f) of Directive 2001/83/EC, where required.

3.5.11 When relevant, the TSE (Transmissible Spongiform Encephalopathy) status of all materials used in batch manufacture is compliant with the terms of the authorisation.

3.5.12 All records are complete and endorsed by appropriate personnel. All required in-process controls and checks have been made.

3.5.13 All manufacturing and testing processes remain in the validated state. Personnel are trained and qualified where required.

3.5.14 Finished product quality control (QC) test data complies with the registered Finished Product Specification, or where authorised, the Real Time Release Testing programme.

3.5.15 Any post marketing commitments relating to manufacture or testing of the product in the authorisation have been addressed. On-going stability data continues to support certification.

3.5.16 The impact of any change to product manufacturing or testing has been evaluated and any additional checks and tests are complete.

3.5.17 All investigations pertaining to the batch being certified (including out of specification and adverse trend investigations) have been completed to a sufficient level to support certification.

3.5.18 Any on-going complaints, investigations or recalls do not negate the conditions for certification of the batch in question.

3.5.19 Required technical agreements are in place.

3.5.20 The self-inspection programme is active and current.

3.5.21 The appropriate arrangements for distribution and shipment are in place.

3.5.22 In the case of human medicinal products intended to be placed on the market in the Union, the presence of the safety features referred to in Article 54 of Directive 2001/83/EC have been verified, where appropriate.

3.6. For certain products, special guidance may apply, such as Annex 3 of the Guide for radiopharmaceuticals.

3.7. Parallel importation and parallel distribution

3.7.1 Prior to certification of a batch the QP should confirm compliance with national rules for parallel importation and EU rules for parallel distribution.

3.7.2 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.

3.7.3 The re-packager should ensure that product intended for repackaging has been obtained from the authorised supply chain and that each sourced batch has undergone certification by a QP prior to its release into the supply chain.

3.7.4 The re-packager must ensure authenticity by verifying safety features, where applicable.

3.8. Recording of the certification

3.8.1 The certification of a medicinal product is recorded by the qualified person 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 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.

3.8.2 The control report referred to in Article 51 of Directive 2001/83/EC or Article 55 of Directive 2001/82/EC or another proof of certification for release to the market in question based on an equivalent system should be made available for the batch in order for the batch to be exempted from the controls when entering another Member State.

4. Relying on GMP assessments by third parties e.g. audits

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

4.1. Relying on assessment by third parties (eg. audits) should be in accordance with Chapter 7 of the EU GMP Guide in order to appropriately define, agree and control any outsourced activity.

4.2. Special focus should be set on the approval of audit reports:

4.2.1 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. API manufacturing, quality control testing, primary packaging, etc. All audited areas should be accurately described resulting in a detailed report of the audit.

4.2.2 It should be determined whether the manufacture and quality control of API and medicinal products follows GMP at least equivalent Article 46 of Directive 2001/83/EC and Article 50 of Directive 2001/82/EC.

4.2.3 In case of outsourced activities compliance with the Marketing Authorisation should be verified

4.2.4 The QP should ensure that a written final assessment and approval of third party audit reports has been made by the company according to the company´s requirements.

4.2.5 Outsourced activities with critical impact on the product quality should be defined in accordance with the principles of Quality Risk Management such as described in Part III of the EU GMP Guide. 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.

4.2.6 Repeated audits should be performed in accordance with the principles of Quality Risk Management.

5. Handling of unplanned deviations

5.1. As long as registered specifications for active substances, excipients and finished products are met, a QP may, taking the following guidance into account, consider confirming compliance / certifying a batch where an unplanned and unexpected deviation from details contained within the Marketing Authorisation and/or GMP has occurred.

5.2. Where a deviation has occurred during manufacture or testing of a batch of finished product it may be considered to meet the requirements of the marketing authorisation and GMP when the details described below have been taken into account:

5.2.1 The deviation is unexpected, unplanned and relates to the manufacturing process and/or the analytical control methods as described in the Marketing Authorisation.

5.2.2 An assessment has been performed by the manufacturer using an appropriate approach such as described in Quality Risk Management in Part III of the EU GMP Guide, and which supports a conclusion that the occurrence does not have an adverse effect on quality, safety or efficacy of the product.

5.2.3 The risk management has evaluated the need for inclusion of the affected batch/ batches in the on-going stability programme.

5.2.4 For biological medicinal products in particular, the risk management has taken into consideration that even minor changes to the process can have an unexpected impact on safety or efficacy.

5.3. The QP performing certification should be aware and take into consideration any deviations which have potential impact for compliance with GMP or the Marketing Authorisation.

6. The release of a batch

6.1. Batches of licensed 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 released it should remain at the site of manufacture or be shipped under quarantine to another authorised site.

6.2. Safeguards to ensure that uncertified batches are not released should be in place and may be physical (via the use of segregation and labelling) or electronic (via 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.

6.3. Notification by a QP to the releasing site that certification has taken place should be formal and unambiguous and should be subject to the requirements of Chapter 4 of the EU GMP Guide.

7. 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.

Bulk production batch: a batch of product, of a size described in the application for a Marketing authorisation, either ready for assembly into final containers or in individual containers ready for assembly to final packs. (A bulk production batch may, for example, consist of a bulk quantity of liquid product, of solid dosage forms such as tablets or capsules, or of filled ampoules, or the first blending of an API and an excipient).

Certification of the finished product batch: the certification in a register or equivalent document by a Q.P., as defined in Article 51 of Directive 2001/83/EC and Article 55 of Directive 2001/82/EC, before a 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, 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 of the finished product, a finished product batch is defined in Part 1 Module 3 point 3.2.2.5 of Directive 2001/83/EC2, and mentioned in Part 2 section F1 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 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 and Article 52 of Directive 2001/82/EC.

Content of the confirmation of the partial manufacturing of a medicinal product / investigational 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 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) of the destination country/countries 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