ANNEX 16

CERTIFICATION BY THE AUTHORISED PERSON AND BATCH RELEASE

SCOPE

This Annex provides guidance on the certification by an Authorised Person and on batch release of medicinal products for human or veterinary use within a Pharmaceutical Inspection Co-operation Scheme (PIC/S) Participating Authority 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 PIC/S Participating Authorities under national law.

Guidance in this Annex on the certification of batches by a manufacturer of a medicinal product is within the scope of the Pharmaceutical Inspection Co-operation Scheme. However, each PIC/S Participating Authority may decide whether guidance expressed in this annex should become a legally-binding standard in relation to imported medicinal products.

This Annex does not address any controls on release of medicinal products by a National Competent Authority under national law (e.g. certain blood and immunological products); however, this Annex does apply to the Authorised Person certification and subsequent release of such batches.

The basic arrangements for batch release for a medicinal product are defined by its marketing authorisation (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 Authorised Person is responsible for ensuring that each individual batch has been manufactured and checked in compliance with national requirements 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 an Authorised Person 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 Authorised Person. 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 PIC/S GMP Guide, Part I, needs to be investigated or a batch recalled, to ensure that any Authorised Persons involved in the certification or confirmation[1] and any relevant records are readily identifiable.

1. THE PROCESS OF CERTIFICATION

1.1. Each batch of finished product must be certified[2] by an Authorised Person before being released for sale, supply or export. Certification can only be performed by an Authorised Person of the manufacturer and/or importer which are described in the MA.

1.2. Any Authorised Person involved in the certification or confirmation of a batch must have detailed knowledge of the steps for which they are taking responsibility. The Authorised Persons 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 Authorised Person 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 national requirements where certification is taking place.

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

2 The contents of a batch certificate for medicinal products are recommended in Appendix II to this Annex. The content of a batch certificate may differ from Appendix II as required under national law or as required to facilitate arrangements between National Competent Authorities.

1.4. Each manufacturing site must have at least one Authorised Person.

1.4.1 Where the site only undertakes partial manufacturing operations in relation to a batch, then an Authorised Person 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 Authorised Person is responsible for providing confirmation of compliance for those operations with the relevant MA, then the Authorised Person should have access to the necessary details of the MA.

1.4.2 The Authorised Person who performs certification of the finished product batch should assume full responsibility for all stages of manufacture of the batch or this responsibility may be shared with other Authorised Persons who have provided confirmation for specified steps in the manufacture and control of a batch. These could be other Authorised Persons who are operating under the same manufacturing authorisation holder or operating under different manufacturing authorisation holders

1.4.3 Any sharing of responsibilities amongst Authorised Persons in relation to compliance of a batch must be defined in a written agreement. 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 jurisdiction of a National Competent Authority, physical importation and certification are the final stages of manufacturing which precede the transfer to saleable stock of the batch, depending on national law.

1.5.1 The process of certification as described in Section 1 of this Annex, applies to all medicinal products intended to be released within domestic markets, or for export, irrespective of the complexity of the supply chain and the global locations of manufacturing sites involved.

1.5.2 In accordance with the principles described in Section 1.4 of this Annex and the law in each jurisdiction, the Authorised Person certifying the finished medicinal product batch may take account of the confirmation by, and share defined responsibilities with, other Authorised Persons in relation to any manufacturing or importation operations taking place at other sites in the same jurisdiction 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 Authorised Person before certification of a batch.

1.5.4 The Authorised Person certifying the finished product is responsible for ensuring that each finished medicinal product batch has been manufactured in accordance with GMP and the MA. The Authorised Person is also responsible for ensuring that the finished medicinal product batch has undergone testing required upon importation in accordance with national law.

1.5.5 If sampling of imported product is necessary, it should be fully representative of the batch. Samples may either be taken after arrival in the jurisdiction of the National Competent Authority, or be taken at the manufacturing site located in

another jurisdiction in accordance with national law and 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 National Competent Authority jurisdiction should be shipped under equivalent transport conditions as the batch that they represent.

1.5.6 Where sampling is performed at a manufacturing site located in another jurisdiction, 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 in the other jurisdiction 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 other jurisdiction are representative of the batch after importation. This study should at least include:

- description of the sampling process in the other jurisdiction;
- description of the transported conditions of the sample and the imported batch. Any differences should be justified;
- comparative analysis of samples taken in the other jurisdiction and samples taken after importation; and
- 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 another jurisdiction.

iv. A review of any unexpected result or confirmed out of specification result. These may have implications for reliance on sampling performed at a manufacturing site located in another jurisdiction and should be notified to the National Competent 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 the PIC/S GMP Guide, Part I.

1.5.7 Different imported finished product batches may originate from the same bulk product batch. If testing upon importation is required (see 1.5.4), the Authorised Person(s) 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 another jurisdiction. 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; and

v. the sample(s) tested are representative of all finished product batches derived from the bulk batch.

1.6 The Authorised Person must ensure that the following operational responsibilities are fulfilled prior to certification of a batch:

i. Certification is permitted under the terms of any authorisation by the national competent authority.

ii. Any additional duties and requirements of national law are complied with.

iii. Certification is recorded in accordance with this Annex and in accordance to national law.

1.7 In addition, the Authorised Person 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 Authorised Person will need to rely on the pharmaceutical quality system and the Authorised Person 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 Authorised Person. 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 Authorised Person performing the certification.

1.7.4 All sites of manufacture, analysis and certification are compliant with the terms of the MA for the intended jurisdiction.

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 ensures only materials of the required quality have been supplied.

1.7.7 For medicinal products, 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 Active substances used in the manufacture of medicinal products for human use shall only be imported if the active substances comply with the following requirements:

i. the active substances have been manufactured in accordance with standards of GMP and, where applicable, distributed in accordance with Good Distribution Practice according to national law; and

ii. there is evidence of GMP compliance of the manufacturer of the active substance in accordance to national law.

1.7.9 The excipients used to manufacture a medicinal product have been manufactured with an appropriate good manufacturing practice. Where applicable, this shall be in accordance with PI 045-1: Guidelines on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use.

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 A batch should not be certified if there are any on-going complaints, investigations or recalls that may have impact on the batch.

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 Where required in national law, safety features have been affixed to the packaging enabling wholesale distributors and persons authorised or entitled to supply medicinal products to the public to:

i. verify the authenticity of the medicinal product;
ii. identify individual packs; and
iii. verify, via a device, of whether the outer packaging has been tampered with.

1.8 For certain products, special guidance may apply, such as PIC/S GMP Guide 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, as applicable under national law.

1.9.1 Prior to certification of a repacked batch the Authorised Person should confirm compliance with national requirements for parallel importation and rules for parallel distribution.

1.9.2 The Authorised Person, who is 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 Authorised Person certification:

1.10.1 The certification of a medicinal product is recorded by the Authorised Person in the document provided for that purpose. The record should show that each production batch satisfies the following provisions:

i. Each batch of medicinal products has been manufactured and checked in compliance with national law and in accordance with the requirements of the marketing authorisation.
ii. In the case of medicinal products coming from another jurisdiction each production batch has 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 in accordance with the requirements of the marketing authorisation. Such testing is also performed in the importing country where required in national law.
iii. In the case of medicinal products imported from another jurisdiction, where appropriate arrangements have been made with the exporting jurisdiction to ensure that the manufacturer of the medicinal product applies standards of good manufacturing practice at least equivalent to those laid down by the national competent authority, and to ensure that the controls referred to under point (ii) have been carried out in the exporting country, the authorised person may be relieved of responsibility for carrying out those controls.

iv. The record must be kept up to date as operations are carried out and must remain at the disposal of the agents of the National Competent Authority the longer of one year after expiry of the batch or five years unless otherwise specified in national law.

1.10.2 The control report referred to in 1.10.1 or another proof for release for sale, supply, or export, based on an equivalent system, should be made available for the batch in order to be exempted from further controls when entering another National Competent Authority jurisdiction.

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

In some cases the Authorised Person 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 PIC/S 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 another jurisdiction, GMP at least equivalent to that of each National Competent Authority.

iii. In case of outsourced activities compliance with the MA should be verified.

iv. The Authorised Person should ensure that a written final assessment and approval of third party audit reports have been made. The Authorised Person 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 Annex 20 of the PIC/S GMP Guide. According to this, the Authorised Person 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, an Authorised Person 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 Annex 20 of the PIC/S 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 Authorised Person involved in the manufacture and control of a batch, the Authorised Person 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 an Authorised Person 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 National 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 Authorised Person certification to the site where the transfer to saleable stock is to take place should be defined within a technical agreement. Such notification by an Authorised Person to the site should be formal and unambiguous and should be subject to the requirements of Chapter 4 of the PIC/S GMP Guide, Part I.

4.4 National law may require a specific release for the local market (market release) by the MAH which takes into consideration the certification of the finished product by the manufacturer.

GLOSSARY TO ANNEX 16

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 PIC/S GMP Guide.

Certification of the finished product batch
The certification in a document by an Authorised Person, as defined in this annex, 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 an Authorised Person 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 Authorised Person responsible for certifying the finished product batch before release. The Authorised Person 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 an entity which comprises all the units of a pharmaceutical form which are made from the same initial quantity of material and have undergone the same series of manufacturing and/or sterilisation operations or, in the case of a continuous production process, all the units manufactured in a given period of time. 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
Any holder of the authorisation to import as required by national law.

Jurisdiction
A jurisdiction is a territory within which a court or government agency is exercising its power. A jurisdiction can be e.g. a State (whether internationally recognised or not) or a region.

APPENDIX I
Recommended 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 PIC/S GMP 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 [insert jurisdiction] 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 Authorised Person confirming the partial manufacturing.

7. Signature of Authorised Person confirming the partial manufacturing.

8. Date of signature.

APPENDIX II
Recommended 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.

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 [insert jurisdiction] and [as applicable] with the requirements of the Marketing Authorisation(s) of the destination country/countries.

5. Name of the Authorised Person certifying the batch.

6. Signature of the Authorised Person certifying the batch.

7. Date of signature.