

New Annex 16: Certification by a Qualified Person and Batch Release

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New Annex 16 – why?

- ▶ 12 October 2015: new Annex 16 shared
- ▶ Deadline for coming into operation: 15 April 2016
- ▶ Reasons for change:
 - ▶ Globalisation
 - ▶ New Quality Control Strategies
 - ▶ Prevention of entry of falsified medicinal products in legal supply chain
 - ▶ Implements ICHQ8, Q9 and Q10
 - ▶ Clarification of parts that were up for interpretation

A first glance

- ▶ Structure of document: less examples, more basic principles
- ▶ More QP responsibilities described
- ▶ Large emphasis on MA holder
- ▶ Two appendices describing text for confirmation and certification statements
- ▶ Less on importation or Mutual Recognition Agreement countries (Annex 21 update - guidance for importers of medicinal products - coming)

General principles - changes

Before describing any QP responsibilities the Annex states the following:

“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).”

MAH or clinical trial application holder

“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).”

QP knowledge - changes

Requirements to QP product knowledge:

“The QPs should be able to prove their continuous training regarding the product type, production processes, technical advances and changes to GMP.”

Previously:

“A Q.P. should maintain his knowledge and experience up to date in the light of technical and scientific progress and changes in quality management relevant to the products which he is required to certify.”

New emphasis to continuous training

QP responsibilities - changes

- ▶ Sections 1.6 and 1.7:
- ▶ *“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.”*

QP responsibilities - changes

“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.”

Now 21 points follow, of which

- ▶ *“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,”*
- ▶ *“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,”*
- ▶ *“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,”*
- ▶ *“The impact of any change to product manufacturing or testing has been evaluated and any additional checks and tests are complete.”*

There used to be 8 points...

Sampling - changes

The final Annex provides for sampling at a third country manufacturing site. A technical justification should include a formal Quality Risk Management process to identify and manage any risks associated with this approach.

During the consultation phase, stakeholders expressed their concerns regarding the sampling of imported products.

Clarity is provided now:

"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. (...) Any samples taken outside the EU should be shipped under equivalent transport conditions as the batch that they represent."

Handling of unexpected deviations

Implementation of the position and solution proposed by EMA related to certification and releasing of the batches where minor deviations concerning the manufacturing process and/or the analytical control methods from details described in the MA occurs

“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.”

Then details on impact assessment follow.

Discussion on the process of certification

- ▶ Section 1.3, 1.4 and 1.5 cover quite some opportunity of delegation and sharing of responsibilities as long as each manufacturing site has a QP and all is agreed and documented.
- ▶ Will this change the way you work?

Discussion on release of a batch

“Batches of medicinal products should only be released for sale or supply to the market after certification by a QP. 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.”

Is this any different from what you are currently doing?

Discussion on content of confirmation of partial manufacturing/batch certificate

- ▶ Are they any different from your statements/certificates?

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.

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.

Discussion on position of certifying QP

- ▶ Current Annex 16:
 - ▶ *“The finished product batch should be certified by a Q.P. of the manufacturing authorisation holder responsible for releasing the batch to the market.”*
- ▶ New Annex 16:
 - ▶ *“Certification can only be performed by a QP of the manufacturer and/or importer which are described in the MA.”*
- ▶ What do you think? Is there a difference?

Back-up slides

All 21 requirements...

- ▶ 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. 6
- ▶ 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.

All 21 requirements...

- ▶ 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.

All 21 requirements...

- ▶ 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. 7
- ▶ 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.

The current 8 requirements

- ▶ a) the batch and its manufacture comply with the provisions of the marketing authorisation (including the authorisation required for importation where relevant);
- ▶ b) manufacture has been carried out in accordance with Good Manufacturing Practice or, in the case of a batch imported from a third country, in accordance with good manufacturing practice standards at least equivalent to EC GMP;
- ▶ c) the principal manufacturing and testing processes have been validated; account has been taken of the actual production conditions and manufacturing records;
- ▶ d) any deviations or planned changes in production or quality control have been authorised by the persons responsible in accordance with a defined system. Any changes requiring variation to the marketing or manufacturing authorisation have been notified to and authorised by the relevant authority;
- ▶ e) all the necessary checks and tests have been performed, including any additional sampling, inspection, tests or checks initiated because of deviations or planned changes;
- ▶ f) all necessary production and quality control documentation has been completed and endorsed by the staff authorised to do so;
- ▶ g) all audits have been carried out as required by the quality assurance system;
- ▶ h) the QP should in addition take into account any other factors of which he is aware which are relevant to the quality of the batch