



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

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GMDP Inspectors Working Group (GMP/GDP IWG)

## Concept paper on Revising Annex 16 of the Guide to Good Manufacturing Practice: Certification by a Qualified Person and Batch Release

<b>Agreed by GMP/GDP IWG</b>	<b>Oct 2011</b>
End of consultation (deadline for comments)	31 January 2012

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## 1. Introduction

Annex 16 of the Guide to Good Manufacturing Practice for Medicinal Products gives guidance on the certification and batch release of medicinal products within the European Union and European Economic Area. Since introduction of the Annex in 2002, the pharmaceutical business environment has changed and new technologies have developed. The supply chains have become quite complicated through globalisation, and new falsified medicines legislation has been approved. Modern control techniques such as Process Analytical Technology, Real Time Release Testing and implementation of ICH Q8, Q9 and Q10 documents, as well as progress in biotechnology and advanced therapy medicinal products, are examples of developments which call for a thorough review of the Annex. In addition there are a number of areas where clarification is required, including the documentation (or equivalent system) to verify that batches moving between Member States have undergone certification, the sampling and testing of batches produced in third countries and dealing with minor deviations from marketing authorisations.

## 2. Problem statement

What is the minimum a Qualified Person (QP) must personally carry out when certifying a batch? What are the prerequisites for relying on statements from persons other than fellow QPs? How is the Control Strategy and the batch certification release process linked? What are the expectations for QPs reviewing batch records manufactured by third parties in third countries? What knowledge should a QP have about the site(s) involved in the manufacturing of a batch? What actions are expected from the QP when a batch cannot be certified and therefore released?

Due to the increased complexity of supply chains the current guidelines on certification and release of batches manufactured either partly or fully outside the EU/EEA have become open to interpretation and to questions like those posed above. This in turn, has led to lack of harmonisation in requirements between member states. In addition due to different interpretation by the various Member States, questions have been raised in relation to the documentation required to accompany batches moving between Member States, sampling and testing of batches produced outside the EU/EEA and dealing with minor deviations from marketing authorisations. New legislation and developments in science and technology have created new areas where further guidance is desired – both by the regulators and the industry.

## 3. Discussion

The pharmaceutical industry has been increasingly outsourcing manufacturing activities and streamlining its processes in relation to medicinal products and the starting materials used in their manufacture. This often leads to a situation where the Qualified Person may be quite far removed from and may have lost personal familiarity with the products and the manufacturing sites. At the same time, illegal actors in the supply chain and falsified medicines have become an increasing threat to public health to the extent, that new legislation and countermeasures were needed. The scope of Annex 16 is to give guidance on QP certification and the release of batches of medicinal products and thus, it should be up-to date with the current trends in the business environment.

Today many medicinal products are manufactured in several sites which are often distant from where the QP is located. However, the responsibilities of the QP have not changed since the relevant articles relating to the QP in the directives were first established – when the QP was normally located at the same site where manufacturing and quality control testing of the batch was carried out.

To maintain at least the originally intended level of control over the batches and to minimise the risk of falsified medicines entering the legal supply chain, the role and involvement of the QP should be re-emphasised and the prerequisites for certification and release of a batch of medicinal product should be clearly and unambiguously determined and communicated to minimise any misinterpretation. Specifically, the extent of personal involvement of the QP versus reliance on quality systems and other personnel particularly needs to be clarified where manufacture takes place at a site which is remote from the QP.

Importation of pharmaceutical finished product manufactured from a third country requires a Manufacturing/Importation Authorisation, both for the site where QP certification takes place and the site to which the batch is physically imported, where these are different. Other than where a Mutual Recognition Agreement (MRA) is in place, it is a legal requirement to test each batch in the EC/EEA before certification by a QP. The requirements for the location of testing ("in a Member State") and the minimum testing requirements for products manufactured in third countries are set out in Article 51.1(b) of 2001/83/EC for human medicinal products and in Article 55.1(b) of Directive 2001/82/EC for veterinary medicinal products. The legislation is silent on whether sampling is understood as part of the testing, but there is guidance in GMP Annex 16.4 and elsewhere in the GMP Guide that at least some samples are taken after importation. The industry has commented that there are a range of interpretations across Member States regarding when and where samples should be taken. The wide range of interpretation has also been seen during inspections of manufacturers in different countries.

The QP's discretion when dealing with minor deviations from the details described in the Marketing Authorisation has been addressed in the Reflection Paper published by EMA. This paper has been misinterpreted in some cases and there are many questions regarding its status. Annex 16 would be an appropriate place to provide guidance on what is understood by certification of compliance with the Marketing Authorisation.

The implications of the new legislation related to active pharmaceutical ingredients (APIs), excipients and finished product to the batch certification and release procedures should be explored, as well as ensuring that the guideline is up-to date concerning investigational medicinal products.

There are a number of additional areas where clarifying guidance regarding the QP is strongly desired e.g.:

- The QP's position in an organisation's structure
- The physical location of the QP
- Independence of the QP from the Head of Production Manager and/or Quality Control
- The QP's role in product defects and related investigations

These questions are, not directly related to the batch certification activity itself, and thus, not in the scope of the current Annex 16. More appropriately, they could be addressed in future revisions of applicable Chapters of the GMP Guide or in the Q&A's section on EMA's website.

## **4. Recommendation**

It is proposed, that an overall revision of Annex 16 of the GMP Guide is undertaken to bring it up-to-date with new legislation, with the positive and negative trends seen in the medicines business environment and with the developments in science and technology. A revision will also serve to harmonise the interpretation of existing legislation and GMP guidance between the Member States.

The scope of Annex 16 is to give guidance on Certification by the Qualified Person of batches of medicinal products and the batch release process. It is recommended, that it is not widened to other GMP areas where the QP has a role. Instead, the expectations on the QPs personal involvement and knowledge of the products and production sites should be strengthened.

## **5. Proposed timetable**

Concept paper for discussion and adoption in IWG: October 2011

Release of Concept Paper for Public Consultation: October 2011

Deadline for comments on Concept Paper: January 2012

First draft of revised Annex 16 for discussion in IWG: May 2012

Agreement of Annex 16 draft guidance in IWG: October 2012

Release of Annex 16 draft guidance for Public Consultation: December 2012

Interested Parties meeting: February 2013

Deadline for comments on Annex 16 draft guidance: End February 2013

Final draft of revised Annex 16 for discussion in GMP/GDP IWG: September 2013

Adoption of revised Annex 16 guidance by European Commission November 2013

## **6. Resource requirements for preparation**

There will be a drafting group with six members (Austria, Finland, France (H), Ireland, UK(H&V) of which one is the rapporteur. The group will meet face-to-face in connection with the GMP/GDP IWG meetings.

One Interested parties meeting dedicated to Annex 16 will be held towards the end of the public consultation, targeted to be held in connection IWG meeting in February 2013.

## **7. Impact assessment**

The industry and GMP inspectors will benefit from more straight forward guidance on batch certification in the increasingly complex environment.

Changes may be necessary to nationally implemented policies in response to the agreed harmonised positions reflected in the new Annex.

## **8. Interested parties**

EMA – GMP/GDP IWG, QWP, BWP

Industry – manufacturers/importers and wholesale distributors of medicinal products

National Competent Authorities

## **9. References to literature, guidelines**

GMP Directives 2003/94/EC and 91/412/EEC

Directives for Medicines 2001/83/EC and Veterinary Medicines 2001/82/EC

Falsified Medicines Directive 2011/62/EU

Clinical Trials Directive 2001/20/EC

Updated GDP Guideline, draft

Guideline on Real Time Release Testing, draft

GMP Guide chapters 1 and 2 drafts

GMP Guide Annex 2 Biological Products and Annex 3 Radiopharmaceuticals (short shelf life products)

GMP Annex 13 Investigational Medicinal Products

Reflection Paper on QP discretion

ICH Q8, Q9 and Q10