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GMP Series

EU-Compliant Batch Release of Medicinal Products

How to Meet the GMP-Requirements of Annex 16 EU GMP Guide

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Excerpt from the GMP Compliance Adviser

Contents

Batch Release

Here you will find answers to the following questions:
- What does a EU-compliant batch release of medicinal products look like and what individual steps does it involve?
- What requirements does it have to meet?
- What requirements apply to imported products?
- What responsibilities does the certifying Qualified Person have and how can he/she fulfil them?
- What support systems are available to the Qualified Person?
- What responsibilities does the certifying Qualified Person have for products fully or partially manufactured by contract manufacturers?
- How can the certifying QP meet the challenges of a complex global product/process flow?

1 Introduction

Within the European Union, every single batch of a medicinal product must be certified for release by a Qualified Person in accordance with Article 48 of Directive 2001/83/EC and corresponding national regulations. This final stage of the procedure for manufacturing and testing GMP-compliant medicinal products is based on the official national and European regulations outlined in chapter 3 *Official regulations*.

In this context, the certifying Qualified Person has a number of clearly defined responsibilities and obligations. These are closely examined in chapter 7 *Certification requirements and certification*.

Because of the global *supply chain* and the widespread *outsourcing* of activities, the product and process flow is becoming more and more complex. Against this backdrop, the certifying QP must employ a number of specific systems in order to manage their comprehensive regulatory responsibility. This applies in particular to the certification of products that are partially or fully manufactured by contract manufacturers. It is then important to differentiate between the countries where the products were actually manufactured:
- inside the European Union
- in a country with a valid mutual recognition agreement (MRA) or
- in a third country without a mutual agreement (a non-EU/non-MRA country).

Chapter 8 describes how the certifying Qualified Person can do justice to this enormous task.

A number of specific problems and special products are examined in chapter 9 *Specific problems and products*.

2 The scope of this chapter

This chapter deals exclusively with the batch release of **medicinal products** – including their import from non-EU countries – and the involvement of a **Qualified Person**.

The release of
- starting materials
- packaging materials and
- other production materials

after the incoming goods inspection by the QC department (release before use during the manufacture of medicinal products) is not examined here.

The batch release of *active pharmaceutical ingredients* is regulated in the EU GMP Guidelines, Part II, Chapter 10.20. This area is examined in detail in Chapter 21 *Active Pharmaceutical Ingredients*. The special responsibility of the Qualified Person with regard to active ingredients that require a manufacturer/import authorisation is also examined there and is not discussed in this chapter.

3 Official regulations

The official regulations for the batch release of medicinal products and the corresponding requirements are based on European stipulations that have to be transposed into national law in all EU Member States. This is mandatory rather than discretionary for all Member States in accordance with the EU treaties. The EU regulations define minimum requirements that can be supplemented, but not diminished by national law.

The **regulatory requirements** that apply to the batch release including batch certification by the Qualified Person are only quoted here, they are not explained or discussed. This should encourage the reader to do the following:

- read about the requirements that emanate from the regulations and are discussed in a detailed and clearly structured way in chapter 6 *Batch release process steps* and chapter 7 *Certification requirements and certification*
- get an overview of the legal situation with regard to the subject in question.

3.1 Directive 2001/83/EC

Directive 2001/83/EC on "… the Community code relating to medicinal products for human use" is also referred to as the "European Medicines Law".

In accordance with Article 41 (c), the applicant for a manufacturing authorisation for medicinal products must have the services of at least one Qualified Person at their disposal. The holder of a manufacturing authorisation must also ensure that the Qualified Person is able to carry out his/her duties. Directive 2001/83/EC also defines the responsibilities and obligations of a Qualified Person.

Directive 2001/83/EC
Article 41 (c)
In order to obtain the manufacturing authorization, the applicant shall meet at least the following requirements: … **c)** have at his disposal the services of at least one Qualified Person within the meaning of Article 48. The applicant shall provide particulars in support of the above in his application.
Article 48 (1)
(1) Member States shall take all appropriate measures to ensure that the holder of the manufacturing authorization has permanently and continuously at his disposal the services of at least one Qualified Person, in accordance with the conditions laid down in Article 49, responsible in particular for carrying out the duties specified in Article 51.

Figure 1 Requirements of Directive 2001/83/EC

Directive 2001/83/EC
Article 51:
(1) Member States shall take all appropriate measures to ensure that the Qualified Person referred to in Article 48, without prejudice to his relationship with the holder of the manufacturing authorization, is responsible, in the context of the procedures referred to in Article 52, for securing: **a)** in the case of medicinal products manufactured within the Member States concerned, that each batch of medicinal products has been manufactured and checked in compliance with the laws in force in that Member State and in accordance with the requirements of the marketing authorization; **b)** in the case of medicinal products coming from third countries, irrespective of whether the product has been manufactured in the Community, that each production 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 in accordance with the requirements of the marketing authorisation.
The Qualified Person referred to in Article 48 shall in the case of medicinal products intended to be placed on the market in the Union, ensure that the safety features referred to in point (o) of Article 54 have been affixed on the packaging. The batches of medicinal products which have undergone such controls in a Member State shall be exempt from the controls if they are marketed in another Member State, accompanied by the control reports signed by the Qualified Persons.
(2) In the case of medicinal products imported from a third country, where appropriate arrangements have been made by the Community with the exporting country to ensure that the manufacturer of the medicinal product applies standards of good manufacturing practice at least equivalent to those laid down by the Community, and to ensure that the controls referred to under point (b) of the first subparagraph of paragraph 1 have been carried out in the exporting country, the Qualified Person may be relieved of responsibility for carrying out those controls.
(3) In all cases and particularly where the medicinal products are released for sale, the Qualified Person must certify in a register or equivalent document provided for that purpose, that each production batch satisfies the provisions of this Article; the said register or equivalent document 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.

Figure 1 Requirements of Directive 2001/83/EC (cont.)

3.2 Directive 2003/94/EC

Directive 2003/94/EC "… laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use" is also referred to as the "European GMP Directive".

The duties and responsibilities of the Qualified Person must be outlined in a job description. The relationship between the Qualified Person and the hierarchical structure of the pharmaceutical company must be specified in an organigram.

In cases of contract manufacturing, the responsibility of the Qualified Person for batch certification must be clearly stated in the contractual agreement between the contract giver and the contract acceptor (contract manufacturer).

5.2 Principle

After a general introduction on the scope of application, Annex 16 makes it unmistakeably clear that during batch release within the EU, each batch of finished medicinal product must also undergo **certification** by a Qualified Person.

Annex 16, Chapter 1.1

Each batch of finished product must be certified[2] by a QP within the EU before being released for sale or supply in the EU or for export. …

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

Figure 11 Principle of batch certification

As proof of certification, and for transfer to a third party (e.g. in cases of contract manufacturing certification), the *Batch Certificate for Medicinal Products* in accordance with Annex 16, Appendix II can be used (see figure 12).

Annex 16, 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.

Figure 12 Content of the Batch Certificate for Medicinal Products

However, it must be made quite clear that the *Batch Certificate* is not a replacement for the entry in the *register* in accordance with Annex 16, Chapter 1.10 which will be discussed in detail in chapter 7.4.

The certification of a medicinal product batch by a Qualified Person allows free transfer of the batch within the EU without the necessity of recertification (e.g. when shipped to another EU Member State). However, the product batch must remain within the EU at all times. If a batch that has already been certified leaves the EU, it must be recertified by a Qualified Person if it is reimported into the EU.

In order to be able to accept a deviation, the following requirements must first be met:

1. The deviation may not be
   - expected
   - predictable
   - planned.
2. The specification of
   - active ingredients
   - excipients
   - packaging materials
   - finished product

   in the marketing authorisation may not be affected by the deviation.
3. The deviation relates to the marketing authorisation or GMP-related details of the
   - manufacturing process or
   - analytical testing.

The unexpected deviation must also have triggered the follow-up action below:

4. Testing if there is an impact on
   - quality
   - safety
   - efficacy

   with a negative result.
5. Consideration of the need for additional tests
   - Influence on the stability: *ongoing stability* of the affected batches
   - Influence on safety and efficacy: in case of biological products each and every deviation has to be evaluated for these aspects
6. Root cause analysis
7. Root cause removal

The Qualified Person can only certify the batch despite the deviation when requirements 1 to 7 are met. The decision-making process must be properly documented.

Regardless of how many QPs take on partial responsibility for a batch, the certifying Qualified Person must inform himself/herself about each deviation and evaluate it if there is the possibility that it could affect

- compliance with the marketing authorisation or
- GMP compliance.

The new Chapter 3 in Annex 16 replaces the EM(E)A Reflection Paper on QP discretion "… on a proposed solution for dealing with minor deviations from the detail described in the MA for human and veterinary products (Rev. 1)" (EMEA/INS/GMP/227075/2008).

7.6 Audits by a third party

Chapter 8 *A challenge: complex product and process flows* describes the significance of the auditing of contract manufacturers during batch certification. Among other things, it focuses on the quality assurance system of the contract company. The certifying Qualified Person must check that the QA system works properly by carrying out audits, for example, to ensure that he/she can rely on the confirmation of the Qualified Person working there.

Chapter 2 of Annex 16 defines special requirements for audits and audit reports in case these are also outsourced to *third parties* by the contract giver.

Delegable activities and associated PQS elements	
Annex 16	PQS element(s)/documents/systems
1.7.1 EU GMP compliance (manufacturing, testing)	• Production/test record (Head of Production/Head of QC signature) • CoC (certifying Qualified Person) • CoA • Qualification of contract manufacturer • Qualification of external test sites • Technical agreements
1.7.2 Knowledge of supply chain	• Diagram • Supplier management • Approved list of suppliers • Management of outsourced activities • Change control
1.7.3 Audits	• Qualification of contract manufacturers • Qualification of external test sites • Qualification of active substance manufacturers • Qualification of contract auditors • Audit management
1.7.4 MA compliance (supply chain)	• Regulatory compliance management • Change control • Approved list • Incoming goods inspection
1.7.5 MA compliance (manufacturing, testing)	• Regulatory compliance management • Change control • Approved list • Incoming goods inspection
1.7.6 MA compliance (suppliers and supplier management)	• Regulatory compliance management • Change control • Supplier qualification • Approved list • Incoming goods inspection
1.7.7 EU GMP/GDP compliance (APIs and API supply chain)	• Qualification of active substance manufacturer • QP declaration • Audit management • Qualification of active substance dealer/distributor • Approved list • Incoming goods inspection
1.7.8 API importation & Written confirmation	• Qualification of the API importer • Technical agreement • Incoming goods inspection
1.7.9 Excipients & appropriate GMP	• Formalised risk evaluation • Qualification of the excipient manufacturer

Figure 29 Identification of essential PQS elements

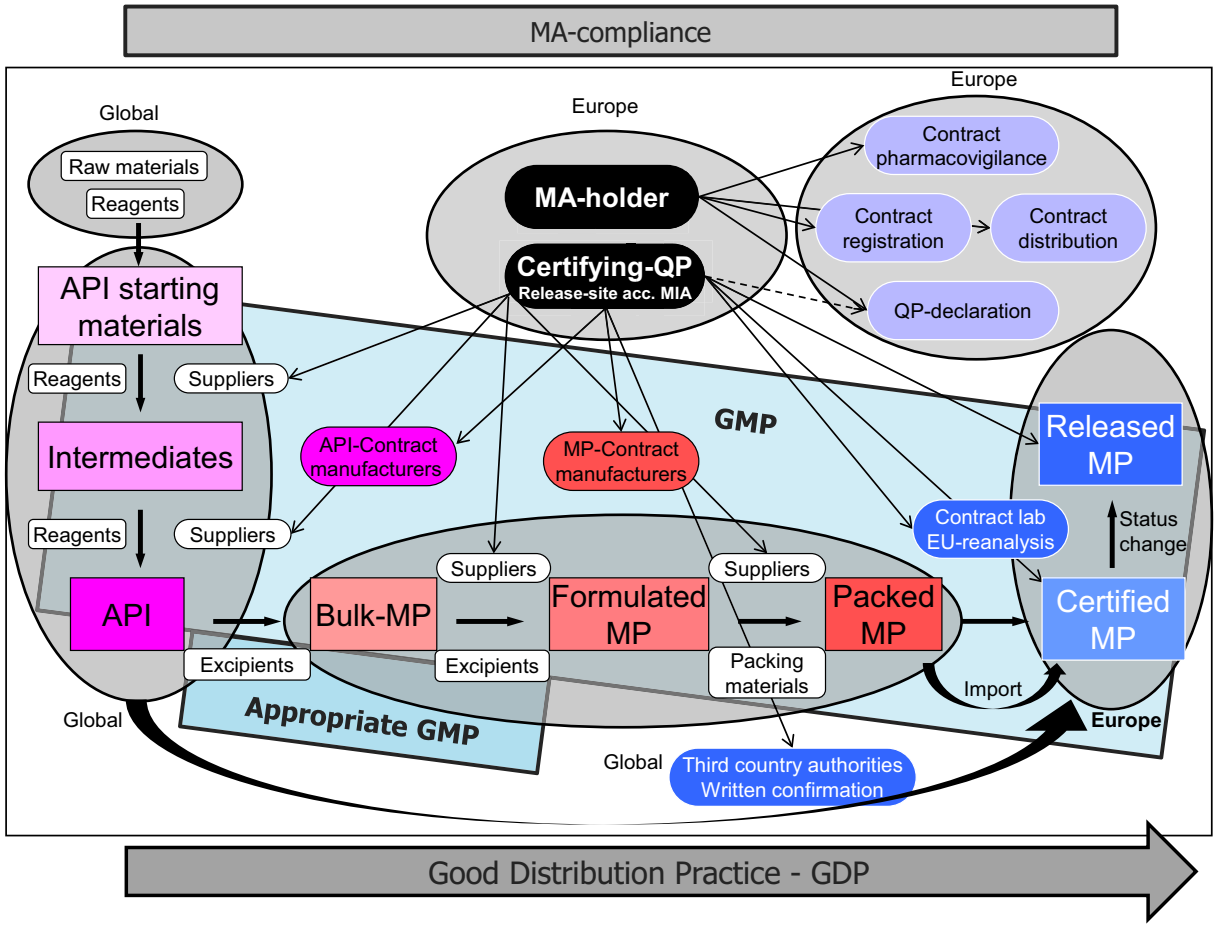

Figure 30 Global product and process flows

The distribution (delegation or outsourcing) of the pharmaceutical responsibilities and activities of the Qualified Person must not only be carried out physically. From the point of view of the certifying Qualified Person, it must also be recorded in *writing and, where applicable, contractually agreed*. Only then can the actual responsibility be demonstrably and legally handed over.

This applies to:
- internal distribution (within an MIA or production site)
- external distribution (different MIAs or production sites)

The required *marketing authorisation compliance* is related to the following components:
- participants in the supply chain (suppliers, contract manufacturers, test operations)
- starting substances and materials
- manufacturing process and analytical testing

Unauthorised modification of just one of these components compromises compliance with the MA.

The more complex the product and product flow becomes, the greater the challenge for the Qualified Person to ensure MA and GMP/GDP compliance for the entire life cycle of the medicinal product.

This can only be achieved using a seamlessly implemented and functioning *change management system*. It must cover all of the participating parties and it must be functional at their respective sites.

If one takes a look at the possible interfaces of this document (see also figure 32) with QA processes that already exist, which primarily include

- supplier management
- the list of approved suppliers
- management of outsourced activities
- regulation-compliance management or
- change control

a graphical representation should not only be created, but also be integrated in a separate PQS element to ensure that the Qualified Person can access, format, maintain and manage it.

The new element should be used for

- comprehensive identification
- full qualification
- continuous knowledge
- continuous control
- management
- coordination
- synchronisation and
- review

of the supply chain and, if required, for regulating/coordinating specific interface problems.

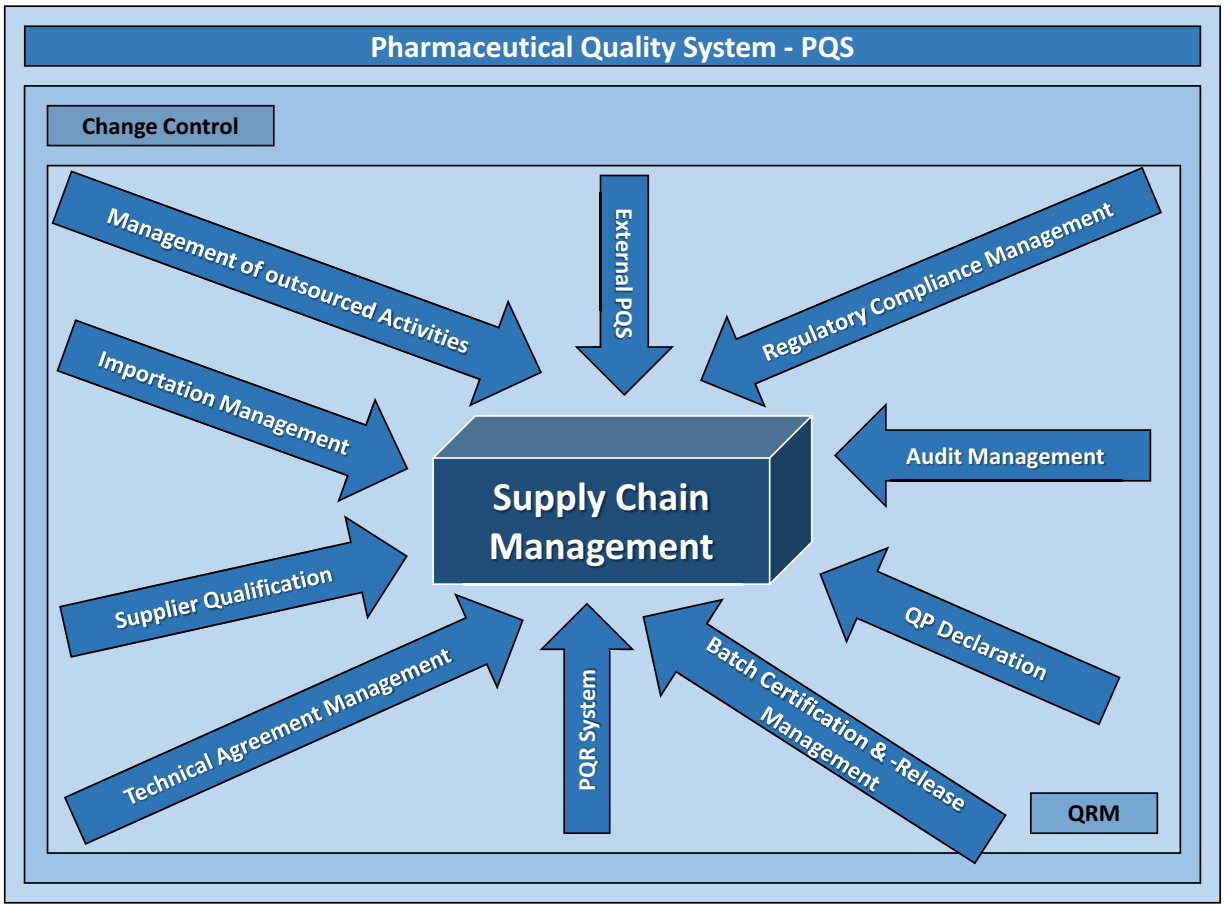

Figure 32 Supply chain management interfaces

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After graduating in Pharmacology and receiving a PhD in Pharmaceutical Technology, Rainer Gnibl managed a retail pharmacy for several years before joining the Pharmaceutical Monitoring Service in 2002. Since then, he has worked for different Bavarian authorities (district governments, Bavarian State Ministry, Bavarian State Office for Health and Food Safety) and currently works for the Government of Upper Bavaria. He lectures at the University and is also deputy chairman of the examination board for the 3rd pharmaceutical state examination. Rainer Gnibl is also a renowned speaker and author.

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