Qualified Person within the European Legislative Framework

John Taylor

Medicines and Healthcare products Regulatory Agency, London (United Kingdom)

Summary

Development of the single market in Europe has been a major step in the move towards harmonising national legislation in regard to medicines. Over the last thirty years the European Community has adopted a number of Directives that require European Member States to implement their provisions nationally, and Regulations that implement EC policy in all Member States without the requirement for national legislation to be enacted. In 2001 many of the medicines Directives were consolidated into two new Directives, 2001/83/EC concerning medicines for human use and 2001/82/EC concerning medicines for veterinary use. The Directives include requirements that Member States ensure that each manufacturer of medicinal products within their territories and each importer of medicinal products manufactured in a third country has at their disposal the services of at least one Qualified Person. The Qualified Person (QP) is appointed by an organisation to carry out specific duties and operations to ensure that each batch of medicinal product has been manufactured, assembled or imported in accordance with relevant legislation. The QP must sign in a register or other record that each batch satisfies the criteria for release for sale, supply or, in some cases, for further processing. There are particular requirements concerning products for use in clinical trials and for active pharmaceutical ingredients. The Qualified Person for Pharmacovigilance is not considered in this paper.

Key words Batch certification · Batch release · Distribution · Good Manufacturing Practice

1. The role and duties of the Qualified Person (QP)

Article 41(c) of Directive 2001/83/EC and Article 45(c) of Directive 2001/82/EC require that an applicant for a manufacturing authorisation shall have at his disposal the services of at least one QP. Articles 49 and 50 of 2001/83/EC and Articles 53 and 54 of 2001/82/EC lay down the academic and experience criteria relating to the QP. A QP designated under the permanent provisions of these Directives is eligible to be named as a QP in any Member State.

The criteria regarding the experience of the QP are that he/she has acquired experience over at least two years in one or more authorised manufacturers in the qualitative analysis of medicinal products, quantitative analysis of active ingredients and of the testing and checking necessary to ensure the quality of medicinal products. Experience gained in a third country manufacturer will not normally contribute towards the required period of experience.

Each batch of a finished medicinal product must be certified by a QP in the Community or EEA before being released for sale or supply in the EC/EEA or for export. This is to ensure that each batch has been manufactured and controlled in compliance with the requirements of the relevant marketing authorisation and manufacturing authorisation and in accordance with the principles and guidelines of EC Good Manufacturing Practice (GMP). Where the batch has been manufactured in a third country the QP should take account of the standards of GMP pertaining in that country and whether they are recognised as equivalent to those in the EC (for example where there is a mutual recognition agreement between that country and the EC) or whether there are other relevant legal requirements.

Before certifying a batch for release the QP should satisfy him/herself that the requirements of the relevant authorisations have been met, that the principles and guidelines of GMP have been observed throughout the manufacture, assembly and testing processes and that the key processes in these areas have been validated. The QP should also ensure that all relevant checks and tests have been performed, including in-process controls and environmental monitoring. Where changes or deviations in manufacturing or quality control have been made, the QP should assess whether they may have an impact on product quality and where necessary he/she should ensure that such changes have been notified to and agreed by the appropriate Regulatory Authority. Any additional checks needed as a consequence of the changes should be considered. The QP should ensure that all relevant documentation has been completed and that necessary reconciliations have been carried out and show no cause for concern.

If the various stages of manufacture and assembly of a medicinal product are undertaken by different companies, there should be a written contract to describe the arrangements for QP certification. The QP acting for the final manufacturer in the chain must have access to all of the relevant information from previous stages to enable his/her responsibilities to be discharged. The QP may also rely on the confirmation by one or more QPs concerning compliance with the relevant requirements at intermediate stages in batch manufacture. Where the marketing authorisation holder is different from the manufacturing authorisation holder and wishes to be responsible for batch release, that organisation's QP must likewise have access to all relevant information from the manufacturer(s). Further information concerning QPs' responsibilities for batches where different stages of manufacture are carried out at different sites, or by different organisations, can be found in Annex 16 of the EC Guide to GMP [1].

The QP does not have to carry out all of the duties associated with batch release personally. He/she may delegate tests and checks to trained, experienced, staff that possess the necessary competences. In these circumstances it is the QP's duty to ensure that necessary work has been carried out and documented. The QP should also be satisfied that an effective, audited, quality management system is in place to provide a level of assurance that will support such delegation. It is also a requirement that the QP is present at the manufacturing site for a sufficient proportion of his/her time to be familiar with manufacturing conditions and the discharge of the delegated duties. Although

the QP may delegate some duties, he/she remains accountable and responsible for certifying batch release. In the case of a contract QP it is expected that there is a formal written agreement between the QP and the organisation which details the various responsibilities. The contract should also state the amount of time that the QP is expected to be on site.

2. QP in investigational medicinal products and active pharmaceutical ingredients

Directive 2001/20/EC requires that Member States ensure that a manufacturer of investigational medicinal products (IMP) holds an appropriate manufacturing authorisation and that the holder has permanently and continuously at his disposal the services of at least one QP. The QP is responsible for ensuring that each batch of IMP manufactured in the EC/EEA has been manufactured and checked in accordance with the principles and guidelines of GMP as laid down in Directive 2003/94/EC. In addition to this the QP should be satisfied that the batch has been manufactured and checked in accordance with the product specification file and that the sponsor of the clinical trial in which the product is to be used has sought the necessary regulatory authorisation for the trial. Where the product is manufactured in a third country the QP must ensure that each batch has been manufactured and checked in accordance with GMP standards at least equivalent to those in the EC/EEA. Where the IMP is a comparator manufactured in a third country, and the assurance above cannot be obtained, the QP must be satisfied that each production batch has been analysed and subjected to the necessary checks and tests to confirm its quality. The duties of the QP for IMPs are laid down in Annex 13 of the EC Guide to GMP [2].

Article 46(f) of Directive 2001/83/EC states that a manufacturer is obliged to use as starting materials only active substances that have been manufactured in accordance with the detailed guidelines on GMP for starting materials. Manufacture of active substances used as starting materials includes both total and partial manufacture, or import of an active substance. A declaration from a QP of a medicinal product manufacturer of compliance of the active substance manufacturer with appropriate standards of GMP is required in support of an application for a marketing authorisation in respect of the product and to support an application to vary a marketing authorisation with regard to a change of starting material manufacturer. There is no requirement for an API manufacturer to have available the services of a QP, but there should be an independent quality unit whose responsibilities include releasing or rejecting APIs.

3. The role of the QP in distribution activities

The QP's responsibilities do not end with authorisation for batch release. The QP has an important role to play in ensuring that product quality is maintained throughout the distribution chain and that activities comply with standards of good distribution practice. With increasing globalisation of medicines distribution, the chain can be complex, involving a number of storage sites, transit sites and transportation systems. According to EC GMPs, the manufacturer's quality assurance system should ensure that satisfactory arrangements exist so that medicinal products are stored, distributed and subsequently handled so that quality is maintained throughout their shelf life. The system should also ensure that all necessary facilities for GMP are provided, including suitable storage and transport.

Legal and Professional Duties of the Qualified Person

Dr. Christopher Burgess

Burgess Consultancy,
Co. Durham
(United Kingdom)

Summary

The following paper addresses the legal and professional aspects of the Qualified Person primarily from a UK perspective. It confines itself to production and control of human medicines for the most part but much of what is discussed is relevant to veterinary and other Qualified Person sectors. Each member state incorporates the EU directives into national legislation and interprets the requirements. It is apparent that the manner in which a person is deemed suitable to perform the duties of the Qualified Person differs between member states.

A brief historical overview of the relevant EU directives is undertaken in order to place the UK procedures in context particularly regarding Articles 48 and 49 of EU directive 2001/83/EC and their relationship to Article 51.

The core of the paper is a discussion of the manner in which the UK has decided to implement the provisions for the Qualified Person in three aspects:

1) The manner of satisfying the qualification, knowledge and experience requirements
2) Eligibility and training
3) A professional code of conduct

The paper concludes with a short discussion of the duties of the Qualified Person both from a legal perspective and the new challenges arising from the changing GXP regulatory climate.

Key words Continuous professional development · EU directives · EU GMP Annex 16 · Qualified person, code of professional conduct, legal and professional duties · UK Medicines Act 1968

1. UK legal overview

The UK has a history of the control of manufacturing and release of pharmaceutical products which predates EU directives 75/318/EEC and 75/319/EEC and its membership of the EU.

The Medicines Act (1968), a direct consequence of the thalidomide tragedy of the early 1960s, is the core legislation in the UK. It introduced the Product and Manufacturing Licensing systems. The Manufacturing Licence is the statutory basis for the specification and control of the quality of medicinal products. This has been amended and extended over the intervening years via the mechanism of the Statutory Instrument. Indeed it is the same mechanism used today to promulgate the EU Directives within UK law.

GMP guidance in the UK was first published in 1971 and was affectionately known as the 'Orange Guide'. This has evolved over the intervening years and was a formative input to the EU GMP Guide of 1987. For more details of these matters see Sharp [1].

The role of the Qualified Person (QP) was explained by the UK authority, The Medicines Control Agency (MCA), via two Medicines Act Leaflets (MAL 45 and 69). These have been subsequently withdrawn and will be replaced by Guidance Note 9 when available. In the event, they have been effectively replaced by a Code of Practice for Qualified Persons in the Pharmaceutical Industry contained in The Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2002 (Medicines Control Agency) [now Medicines and Healthcare Products Regulatory Agency, MHRA]. This and other aspects of the role of the Professional Bodies in the UK will be discussed later.

2. European Directives

The EU Directives are complex but have evolved from a single founding directive 65/65/EEC. The complexity is such that it is useful to track the essential aspects of their development in a simplified form as shown in Fig. 1.

The incorporation into UK law has been briefly described in the previous section.

The codification directive 2001/83/EC has been chosen as the focus for the diagram because it provides the consolidation point of the historical requirements from 65/65/EEC and a natural route to the extending and modifying directives currently in place.

For those Qualified Persons who were 'in post' and subject to the transitional arrangements of 75/319/EEC and its companion 75/318/EEC were formative in shaping the way in which Qualified Person arrangements were developed.

Article 48 of 2001/83/EC is pivotal to the present discussion of legal and professional duties as it links both to the qualification requirements for (Article 49) and the statutory duties of (Article 51) the Qualified Person. The relevant sections are quoted below (Note: words in bold are the author's for emphasis and not in the regulation).

Article 48 of 2001/83/EC

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.*

Article 49 of 2001/83/EC (Article 23 of 75/319/EEC)

Member States shall ensure that the qualified person referred to in Article 48 fulfils the following ***minimum*** *conditions of qualification: Possession of a diploma, certificate or other evidence of formal qualifications awarded on completion of a university course of study, or a course recognized as equivalent by the Member State concerned, extending over a period of* ***at least four years*** *of theoretical and practical study in one of the following scientific disciplines: pharmacy, medicine, veterinary medicine, chemistry, pharmaceutical chemistry and technology, biology. However: the minimum duration of the university course may be three and a half years where the course is followed by a* ***period of theoretical and practical training*** *of a minimum duration of one year and including a training period of at least six months in a pharmacy open to the public, corroborated by an examination at university level.*

The course shall include theoretical and practical study bearing upon at least the following basic subjects:

- Applied physics
- General and inorganic chemistry
- Organic chemistry
- Analytical chemistry
- Pharmaceutical chemistry, including analysis of medicinal products
- General and applied biochemistry (medical)
- Physiology
- Microbiology
- Pharmacology
- Pharmaceutical technology
- Toxicology
- Pharmacognosy (medical aspects) (study of the composition and effects of the active principles of natural substances of plant and animal origin).

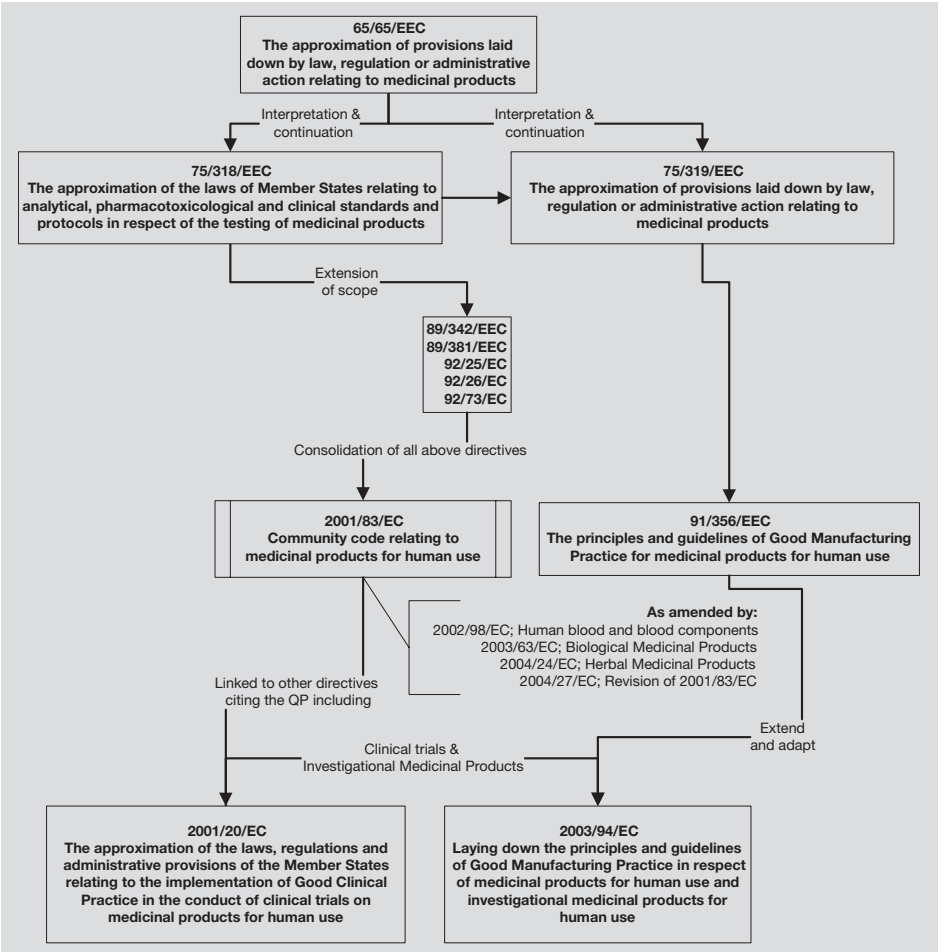

Fig. 1: Flow diagram of key EEC & EU Directives related to 2001/83/EC; Community code relating to medicinal products for human use.

Delegating and Differentiating the Responsibility of a Qualified Person

Ines Janssen, Ph.D.

Baxter AG,
Vienna (Austria)

Summary

Often a batch has different stages of production or testing conducted at different locations or by different manufacturers. An intermediate or bulk production batch may be divided into more than one finished product batch. In these cases delegating of the responsibility of a Qualified Person (QP) is necessary mostly based on Quality Agreements between the different sites / QPs. Annex 16 to the EU GMP Guide defines the responsibilities of a QP in such cases in detail.

Special requirements have to be followed if products are imported from third countries outside the EC/EEA. Is a Mutual Recognition Agreement (MRA) in place the import from that country is much simplified.

Key words Annex 16 · Batch release · Mutual Recognition Agreement (MRA) · Production, different sites · Qualified Person

1. Introduction

Annex 16 to the EU GMP Guide "Certification by a Qualified Person and Batch Release" covers in particular those cases where a batch has had different stages of production or testing conducted at different locations or by different manufacturers. It also describes how to proceed when an intermediate or bulk production batch is divided into more than one finished product batch. In addition it covers the release of batches which have been imported to the EC/EEA both when there is and is not a Mutual Recognition Agreement (MRA) between the Community and the third country. The possible scenarios are:

1) Batch testing and release of products manufactured in EC/EEA
2) Batch testing and release of products imported from a third country
3) Batch testing and release of products imported from a third country with MRA

The duties of the Qualified Person (QP) are fully described in Article 51 of Directive 2001/83/EC, and can be summarized as follows:

a) For medicinal products manufactured within the EC a QP ensures that production and testing is in accordance with the directives and the marketing authorization.

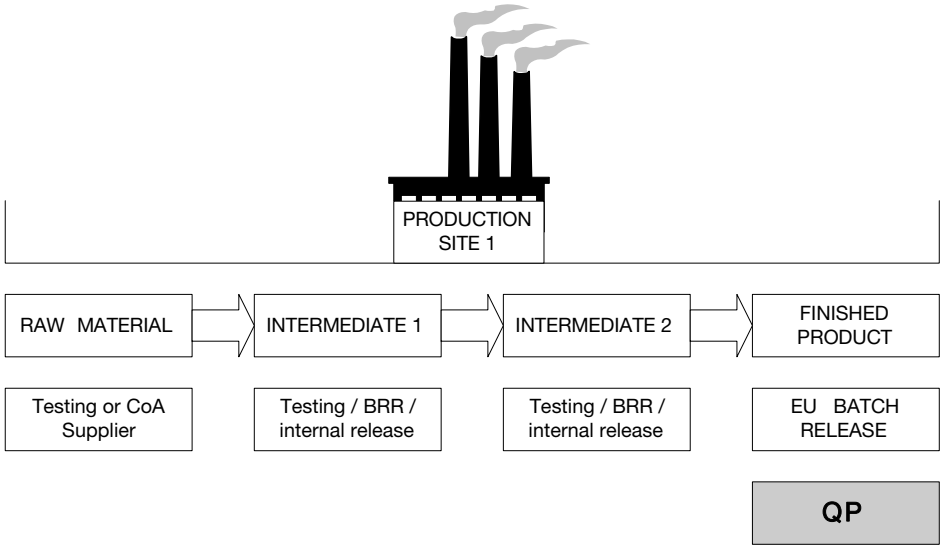

Fig. 1: All manufacture occurs at a single authorised site.

b) For medicinal products manufactured outside the EC a QP ensures that each imported batch has undergone, in the importing country, the testing specified in paragraph 1 (b) of Article 51.

The QP must meet the qualification requirements laid down in Article 49 of Directive 2001/83/EC. The QP shall be permanently and continuously at the disposal of the holder of the Manufacturing Authorisation to carry out his responsibility. *The responsibility of the QP may be delegated, but only to other Qualified Person(s).*

2. Batch testing and release of products manufactured in EC/EEA

There are several different scenarios for batch testing and release of products manufactured in the EC/EEA described in Article 5 of Annex 16. The following possible scenarios can be differentiated.

2.1. All manufacture occurs at a single authorised site

This is the most simple scenario where the QP has direct influence to the Quality Systems of the manufacturing site (Fig. 1). The QP who certifies the finished product batch normally retains personal responsibility for these within a defined system.

Certain checks and controls may be delegated to other people within the quality organization. Special trained quality employees on the floor may perform the batch record review, may sign environmental monitoring reports and critical systems reports. Analytical test protocols may be signed by lab supervisors. Deviation investigation reports may be signed by quality assurance employees. Only the last signature certifying the batch release has to be performed by the QP. This last signature cannot be delegated.

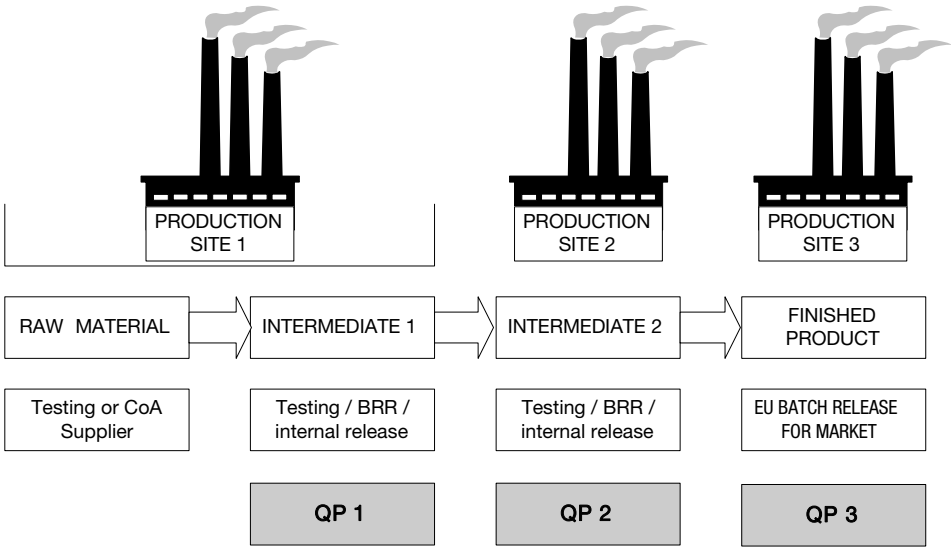

Fig. 2: Different stages of manufacture at different sites within the same company.

2.2. Different stages of manufacture at different sites within the same company

The QP of the marketing authorization holder who certifies the finished product batch retains personal responsibility for all stages (Fig. 2). He may take account of the confirmation of earlier stages by the relevant QPs responsible for those stages. Even if the manufacture is within the same company there should be a QP at each production site certifying the release of the relevant intermediate products. Finally the QP certifying the finished product batch can rely on them. In addition a quality agreement would be very helpful in defining the responsibilities even if manufacture occurs within the same company and a quality agreement is not required by the EU GMP Guide Annex 16.

2.3. Some intermediate stages of manufacture contracted to a different company

In this scenario the QP of the contract acceptor has to confirm the relevant stage and a Quality Agreement is required to define the relevant responsibilities (Fig. 3).

The QP of the marketing authorization holder certifies the finished product batch and may take account of the confirmation by the QP of contracted stage.

2.4. A bulk production batch assembled at different sites into several finished product batches which are released under a single marketing authorisation

In this case there are two possible certification scenarios (Fig. 4):

- The QP of the bulk production site certifies all finished product batches and relies on confirmation of assembly by the QPs of the assembly sites.
- The QP of final assembly site certifies the finished product batch and relies on the confirmation of the QP of bulk production.