QUALIFIED PERSONS IN THE PHARMACEUTICAL INDUSTRY

STUDY GUIDE

GUIDE TO THE KNOWLEDGE AND PRACTICAL EXPERIENCE REQUIRED BY QUALIFIED PERSONS IN THE PHARMACEUTICAL INDUSTRY

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Guide to the Knowledge and Practical Experience Required by Qualified Persons in the Pharmaceutical Industry

Study Guide

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Preface

The three UK professional bodies administering the Qualified Persons scheme, The Institute of Biology, the Royal Pharmaceutical Society of Great Britain and the Royal Society of Chemistry, first introduced a Study Guide for Qualified Persons in 1978 based on Article 23 of 75/319/EEC. A revised version (Study Guide 2000) was issued in 2000, with a further revision in 2004. This present version, the Study Guide 2006, came into effect on **1 May 2006**.

The three professional bodies require an applicant for certification as a Qualified Person to demonstrate foundation knowledge and to be able to apply his or her knowledge of QMS principles, and will also be expected to demonstrate understanding of the additional knowledge requirements. The applicant will be required to demonstrate this by reference to the products and processes for which he or she is claiming his or her qualifying experience, which will apply wholly or in part to the Manufacturer's Licence(s) detailed on the application.

The three professional bodies have determined that the foundation knowledge elements are:

- pharmaceutical law and administration;
- the role and professional duties of the Qualified Person;
- quality management systems (i.e. the basic philosophy and principles of Quality Assurance); the latter applies to all sections of this guide.

Certification of eligibility for nomination as a Qualified Person on a Manufacturer's Licence is dependent upon the demonstration of both an appropriate knowledge of those activities and disciplines relevant to pharmaceutical manufacturing and Quality Assurance (QA), and appropriate practical experience.

1.0 The Qualified Person in the Pharmaceutical Industry: Background

The Medicines and Healthcare products Regulatory Agency (MHRA) of the UK Department of Health, and the Veterinary Medicines Directorate (VMD), have interpreted the requirements of the Pharmaceutical Directive 2001/83/EC and the Veterinary Directive 2001/82/EC through a Study Guide, drawn up by a panel of experts, and have given authority to three professional bodies, the Institute of Biology, the Royal Pharmaceutical Society of Great Britain and the Royal Society of Chemistry, to operate an assessment procedure for their members. The assessments seek to determine an applicant's suitability for being named on a company Manufacturer's Licence.

The professional bodies' role is to certify the eligibility of the applicant for nomination as a Qualified Person on a Manufacturer's Licence. The applicant must be able to demonstrate that he or she can satisfy the knowledge and experience requirements of Articles 49 and 50 of the "Pharmaceutical Directive" 2001/83/EC (amended by Directive 2004/27/EC), Articles 53 and 54 of the "Veterinary Directive" 2001/82/EC (amended by 2004/28/EC), or Article 13 of the "Clinical Trials Directive" 2001/20/EC. Acceptance of a person, certified as eligible for nomination, on a Manufacturer's Licence is a matter for the Licensing Authority.

The certification process includes submission of a completed application form, the sponsorship of an applicant by a Qualified Person who is also a member of the Institute of Biology, the Royal Pharmaceutical Society of Great Britain or the Royal Society of Chemistry, the payment of an application fee, and for applications under the permanent provisions, an oral assessment of the applicant's knowledge and experience.

Applications under the transitional provisions of Article 50 of 2001/83/EC do not normally involve an oral assessment (Since the change in veterinary legislation in 2005, applications can no longer be made under the transitional provisions of 2001/82/EC).

Since 1992 the oral assessments have been conducted jointly by the three professional bodies. The oral assessment is carried out by a panel of assessors drawn from all three professional bodies, who are themselves well-acquainted with the role of a Qualified Person. The three professional bodies have agreed with the MHRA that, in principle, an individual who has been certified as eligible for nomination as a Qualified Person is also potentially eligible for transfer from one Manufacturer's Licence to another, although the final decision for accepting a person as a Qualified Person on a licence rests with the Licensing Authority in the UK. In consequence the assessors must be satisfied that an applicant, after a suitable induction period, will be able to function as a Qualified Person in any licensed undertaking.

Appeals can be made by applicants to their professional body as appropriate.

A guide to the body of knowledge required by the Qualified Person is set out in the following pages. This document should be studied in conjunction with the current edition of the Medicines and Healthcare products Regulatory Agency's (MHRA) "Rules and Guidance for Pharmaceutical Manufacturers and Distributors (known as "the Orange Guide").

The Joint Professional Bodies no longer issue a "Sources of Reference" document. Frequent legislation changes result in the document rapidly becoming out-of-date. Applicants are reminded that a thorough understanding of current legislation is required to meet the requirements of this Study Guide.

2.0 The three foundation knowledge elements

a Pharmaceutical law and administration

To assure patient safety the manufacture and distribution of pharmaceutical products is highly regulated within the European Union. The Qualified Person, in particular, must ensure that all legislative obligations are fully satisfied before any product is released for sale.

A Qualified Person must have a comprehensive knowledge of all European and National legislation relating to the manufacture, storage and supply of licensed medicinal products and the interpretation of the law as exemplified in the current edition of the MHRA's "Rules and Guidance for Pharmaceutical Manufacturers and Distributors ", ("the Orange Guide").

Applicants will be expected to demonstrate a thorough understanding of the following:

- European pharmaceutical directives (including but not limited to 2001/83/EC, 2001/82/EC, 2001/20/EC, 2003/94/EC, 2004/24/EC, 2004/27/EC, 2004/28/EC);
- the UK Medicines Act (1968), and other UK national medicines and veterinary legislation, including amendments;
- Marketing, Manufacturing and Wholesaler Authorisation requirements and responsibilities;
- the role, legal status and structure of both the European and British Pharmacopoeias;

- the organisation of the UK MHRA, the role of the European Agency for the Evaluation of Medicinal Products (EMEA), and the role of the Veterinary Medicines Directorate (VMD);

- procedures for dealing with complaints and product recalls and the role of the MHRA's Defective Medicines Reporting Centre;

- The International Conference on Harmonisation (ICH) guidelines;

- Mutual Recognition Agreements (MRAs);

- Pharmaceutical Inspection Co-operation Scheme (PICS);

b The role and professional duties of a Qualified Person

It is incumbent upon all Qualified Persons, whether or not members of one of the three professional bodies, that they discharge their professional duties in accordance with the Code of Practice for Qualified Persons, which the three professional bodies (IOB, RPSGB and RSC), in collaboration with the MHRA and VMD, have produced.

It is the responsibility of the Qualified Person to certify that a product has been manufactured in accordance with its Marketing Authorisation, and with Good Manufacturing Practice (GMP).

The Qualified Person might not have direct line responsibility for many of the activities which could affect compliance with GMP or the Marketing Authorisation. However, they must be aware of any incidents or deviations which may influence their decision to release a batch for sale.

Applicants will be expected to demonstrate a thorough understanding of the following:

- batch review and decision making on disposition.

- the principles and practice of current GMP and QA as given in European Directives and Guides on Good Manufacturing Practice including relevant Regulations made under the Medicines Act 1968 and the current edition of the MHRA's Guidance for Pharmaceutical Manufacturers and Distributors, ("the Orange Guide");

- the conduct and obligations of MA and MAA holders;

- the preparation for and management of Regulatory Inspections.

c Quality management systems

The manufacture of pharmaceutical products requires the establishment and implementation of an effective 'quality management system' (QMS). The concepts of QA, GMP and Quality Control (QC), which are inter-related, form the basis of such a system for the manufacture of pharmaceutical products.

Applicants will be expected to demonstrate a thorough understanding of the following:

- the philosophy and basic principles of QA;

- the design criteria for an effective QMS;
- auditing and self inspections;
- deviations and change control;
- documentation and record keeping;
- the interpersonal skills (leadership, delegation, communication, etc) necessary to implement an effective QMS;
- the concepts associated with risk management;
- the principles of design, selection, qualification and maintenance of premises, equipment, utilities, and services;
- calibration, preventative maintenance and training;
- the principles of purchasing and supplier certification, including knowledge of supply chains and material control and the roles of brokers, distributors and repackagers;
- production planning, scheduling, and inventory control;
- the interface between QA and the Development, Regulatory Affairs, and Marketing Departments;
- the skills and competences needed to provide effective Good Pharmaceutical Manufacturing Practice training;
- organisational structures and reporting relationships;
- technical agreements and auditing in contract giving and acceptance.

3.0 Additional knowledge requirements for the Qualified Person

d Mathematics and statistics

The practical application of basic statistical tools in pharmaceutical production and QA is essential in demonstrating the capability of processes or the acceptability of materials.

Applicants will be expected to demonstrate an understanding of the following:

- Statistical Process Control;
- BS6000-6001 (Sampling plans);
- Process Control Charts;
- Acceptable Quality Levels (AQLs) (subset of 6001/2);
- statistics applied during analytical method validation.

e Medicinal chemistry and therapeutics

The Qualified Person must have an understanding of the actions and uses of medicines in clinical practice in order to judge their significance for the manufacture of sales material or clinical trial supplies. Evaluating the significance of cross-contamination hazards or product complaints are examples where such knowledge is important.

Applicants will be expected to demonstrate an understanding of the following:

- basic physiology;
- outline knowledge of the autonomic nervous system and some general aspects of chemical structure/pharmacological action relationships;
- summary of key therapeutic drug classifications with examples;
- examples of disease states and their treatment with medicinal products;
- general absorption, distribution, metabolism and excretion of drugs;
- principal routes of drug administration;
- role of the company medical department;
- pharmacovigilance related to quality monitoring;
- general implications of clinical knowledge of drugs upon facility design, plant segregation/isolation, cleaning verification and production scheduling.

f Pharmaceutical formulation and processing

The formulation and processing conditions employed in the manufacture of medicinal products have a significant effect upon their safety, quality and efficacy. Even subtle changes to the input materials and/or processing conditions can have a profound adverse effect on content uniformity, stability, bioavailability, and other attributes which are not detectable by routine QC testing.

It is vitally important that the Qualified Person understands the principles of formulation and pharmaceutical processing to ensure that informed release decisions are made.

Applicants will be expected to demonstrate an understanding of the following:

- the major processing techniques, their limitations and critical control parameters;
- the factors that could potentially affect content uniformity, stability (chemical, physical and microbiological) and bioavailability in manufacture;
- the principles of process validation and control;
- the principles of technology transfer and production scale-up;
- pre-formulation studies and product development;

- the storage and distribution of materials and finished products.

g Pharmaceutical microbiology

The Qualified Person must understand the significance of the presence of bacteria, yeasts, moulds, viruses and toxins in pharmaceutical raw materials, products and production environments. In addition, they must understand how to prevent contamination by good product design, GMP and control over starting materials, intermediates, finished products, production plant and processes, people and the environment.

Applicants will be expected to demonstrate an understanding of the following:

- sources and types of micro-organisms as related to pharmaceutical production;
- production of sterile and non-sterile products and associated environmental controls;
- bacterial endotoxins and pyrogens, their sources, removal and testing;
- microbiology of water, its production and distribution systems;
- sterilisation and disinfection methods;
- interpretation of microbiological data;
- validation of microbiological test methods;
- microbiological specifications;
- selection and use of preservatives;
- microbiological test methods used in routine manufacture and product development;
- rapid methods of microbiological testing.

h Analysis and testing

The sampling and testing of materials does not by itself assure product quality. It must be seen as one part of a comprehensive 'Quality management system', including QA and GMP, which must be correctly implemented and controlled.

The data generated by laboratory testing of samples must be evaluated before materials are released for sale.

Applicants will be expected to demonstrate an understanding of the following:

- GCLP (Good Control Laboratory Practice);
- quality control of sterile and non-sterile dosage forms;
- interpretation of analytical data and non-conforming results;

- the principal qualitative and quantitative analytical methods in common use;
- analytical chemistry as relevant to the properties of medicinal products and materials;
- the principles of method selection and validation;
- the design of sampling regimes;
- biological test methods and interpretation of results;
- physical and organoleptic testing;
- stability testing (protocols & methods);
- the significance of degradation, contamination and adulteration of pharmaceutical materials;
- the types, purpose, significance and management of systems of in-process control;
- the International Conference on Harmonisation (ICH) for method validation and stability testing.

i Pharmaceutical packaging

It is a requirement of GMP that holders of Manufacturing Authorisations establish procedures for their packaging operations to minimise the risk of cross-contamination, mix-up or substitutions. The Qualified Person must understand the importance of controlling packaging components (both primary and printed materials) throughout the supply chain to assure the quality of finished products.

Applicants will be expected to demonstrate an understanding of the following:

- control of packaging components by suppliers and throughout production;
- the chain of systems which ensure the integrity and accuracy of textual information from originator to routine production;
- the layout and organisation of packaging operations;
- causes of label and other printed component mix-ups;
- packaging and labelling processes and equipment;
- the testing of packaging materials including pack integrity testing;
- product security (automated systems, reconciliation, line clearance etc);
- in-process controls;
- effects of packaging materials on product stability;

- selection of packaging materials;
- tamper-evidence and anti-counterfeiting measures.

j Active pharmaceutical ingredients

The Qualified Person must understand the influence of manufacturing pathways and associated physical and physico-chemical attributes, of both active pharmaceutical ingredients and major excipients, on the quality of the finished dosage form.

Applicants will be expected to demonstrate an understanding of the following:

- the steps commonly taken in the synthesis of active pharmaceutical ingredients and excipients (including biopharmaceuticals), their purpose and limitations;
- the generation of impurities, their identification, quantification, and elimination;
- the physico-chemical and biological properties of active pharmaceutical ingredients, and excipients, and their effect on the attributes of the final dosage form;
- the specific requirements for bulk materials intended for sterile products;
- the nature of controls for the manufacture of bulk biological and biotech products;
- auditing of API manufacturers.

k Investigational medicinal products

The manufacture, packaging and distribution of investigational medicinal products must be controlled. There are significant differences between the manufacture of IMPs and licensed dosage forms. The Qualified Person must understand these differences together with the safeguards required to assure the quality of IMP supply.

Applicants will be expected to demonstrate an understanding of the following:

- specific GMPs associated with the manufacture of investigational medicinal products;
- the control of active and placebo forms;
- the control of packaging operations and blinding;
- the control and release of imported IMPs;
- the control and release of comparators;
- effective batch documentation, sampling and batch release;
- change control and material traceability;

- controls surrounding the procurement of Clinical Trial (CT) supplies;
- the principles of clinical trial design and Good Clinical Practice (GCP).

4.0 The Qualified Person: practical experience requirements

The precise wording used in Article 49 of the Pharmaceutical Directive 2001/83/EC is as follows:

"The qualified person shall have acquired practical experience over at least two years, in one or more undertakings which are authorised to manufacture medicinal products, in the activities of qualitative analysis of medicinal products, of quantitative analysis of active substances and of the testing and checking necessary to ensure the quality of medicinal products".

The three professional bodies have interpreted this legal obligation as requiring the applicant to have had at least #one or two years of relevant practical experience in assuring the quality of medicinal products during their manufacture, including Good Manufacturing Practice, as defined in the current edition of the MHRA's "Rules and Guidance for Pharmaceutical Manufacturers and Distributors ("the Orange Guide").

(#In the UK, the MHRA and VMD have approved one year of practical experience for pharmacists).

4.1 Illustration of requirements

Applicants may find the following information helpful in further understanding the expectations of the professional bodies and of the knowledge and practical experience requirements which need to be satisfied.

The professional bodies will seek demonstration of the following:

1. The applicant must have had at least #one/two years relevant practical experience in one or more of those activities embraced by the term QA (as defined and detailed in the EC Good Manufacturing Practice Guide, and the EC Directive 2001/83/EC) gained in premises licensed for the manufacture of medicinal products.

   (#In the UK, the MHRA and VMD have approved one year of practical experience for pharmacists).

   The MHRA advises that experience obtained in an establishment that has only a Specials Licence, or experience of the manufacture of active pharmaceutical ingredients, cannot contribute to the practical experience requirement (unless the site holds a manufacturer's licence) (Article 40 of 2001/83/EC).

   The applicant must demonstrate a thorough core competence in the manufacturing processes and the quality management systems involved in the production, testing, batch release and approval for sale of the products made under the Manufacturer's Licence(s) under which he or she is claiming his or her qualifying experience.

2. In addition, it is important that the applicant can demonstrate an ability to translate and extrapolate the working knowledge and understanding gained from his or her experience. In

particular, scenario questions may be used to determine whether an applicant is able to articulate a logical approach to a practical situation with which he or she may be unfamiliar, thereby demonstrating his or her ability to apply his or her knowledge and experience.

The applicant can expect detailed questioning on his or her knowledge of QMS principles, and will be required to demonstrate this by reference to the products or processes operating under the Manufacturer's Licence(s) under which he or she is claiming his or her qualifying experience.. The assessors may ask questions pertinent to other activities or functions which they consider relevant. The assessors must satisfy themselves that the applicant, after a suitable induction period, will be able to function as a Qualified Person in any licensed undertaking.

5.0 Role of the Qualified Person

5.1 Directives 2001/83/EC and 2001/82/EC

The functions of a Qualified Person as set out in the UK Statutory Instruments and EU Directives 2001/83/EC and 2001/82/EC are as follows:

- to ensure that each batch of the medicinal product to which the licence relates has been manufactured or assembled and checked in compliance with the provisions of the Act and Regulations made there under, the provisions of the Manufacturer's Licence and the provisions of the Product Licence which relates to the product;

- to certify in a register, or other record appropriate for the purpose, whether each production batch of the medicinal product to which the licence relates satisfies the requirements set out above and to ensure that such register or other record is regularly maintained, in particular that the appropriate entries in such register or other record are made as soon as practicable after each such batch has been manufactured;

- for medicinal products manufactured outside the European Community, the Qualified Person must ensure that each imported 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 (although it should be recognised that there are exemptions to this requirement: batches of medicinal products which have undergone such controls in a Member State shall be exempt from the above controls);

- 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 GMP at least equivalent to those laid down by the Community and to ensure that the controls referred to above have been carried out in the exporting country, the Qualified Person may be relieved of responsibility for carrying out those controls.

5.2 Directive 2001/20/EC

The functions of a Qualified Person as set out in the Clinical Trials Directive 2001/20/EC are as follows:

For IMP manufactured in the Member State concerned, that each batch of medicinal product has;

- been manufactured and checked in compliance with the requirements of Directive 2003/94/EC laying down the principles of good manufacturing practice for medicinal products for human use and investigational medicinal products for human use, the product specification file and the information notified pursuant to article 9(2) of Directive 2001/20/EC;

- in the case of an investigational medicinal product manufactured in a third country, that each production batch of product has been manufactured and checked in accordance with standards of good manufacturing practice at least equivalent to those laid down in Directive 2003/94/EC, in accordance with the product specification file and that each production batch has been checked in accordance with the information notified pursuant to article 9(2) of Directive 2001/20/EC;

- in the case of an investigational medicinal product which is a comparator product from a third country and which has a Marketing Authorisation, where the documentation certifying that each production batch has been manufactured in conditions at least equivalent to those laid down in Directive 2003/94/EC, that each production batch has undergone all relevant analyses, test or checks necessary to confirm its quality in accordance with information notified pursuant to article 9(2) of Directive 2001/20/EC.

The role of the Qualified Person is thus of considerable importance within the industry and this should be reflected in the calibre of applicant appointed to such a position. Although every person included in the Register meets, in the opinion of the professional body concerned, the statutory requirements to become a Qualified Person, it is up to individual companies to satisfy themselves of the suitability of any individual applicant for a particular post.

The Licensing Authority is the final arbiter of who can be named as a Qualified Person on a Manufacturer's Licence.

6.0 Other European Member States

Applicants from other EU Member States, who are not members of either of the three aforementioned professional bodies, but who hold an appropriate qualification as defined in Article 49 of 2001/83/EC, are advised to make an application for certification of their eligibility for nomination as Qualified Persons to the UK MHRA.

The Royal Society of Chemistry (RSC) has an agreement with the Institute of Chemistry of Ireland (ICI) that Irish applicants will be assessed by a team of assessors that will include an Irish assessor, who is a member of both the RSC and ICI.

7.0 Summary

In Summary, the applicant must demonstrate:

- the relevant practical experience in one or more licensed facilities;
- an in-depth working knowledge and understanding, allied to practical experience;
- a thorough understanding of the principles and requirements laid out in "the Orange Guide";
- an ability to translate those principles and requirements to other situations currently outside his or her direct experience;
- an endorsement of his or her credentials, including qualifications and experience, from a sponsor.