MHRA

Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2007

Pharmaceutical Press

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Compiled by the Inspection and Standards Division of the Medicines and Healthcare products Regulatory Agency

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Contents

Preface to the 2007 edition

Since the 2002 edition of Rules and Guidance for Pharmaceutical Manufacturers and Distributors (the "Orange Guide") there have been many changes and additions to the detailed European Community guidelines on Good Manufacturing Practice (GMP). In addition, there is a new Directive dealing specifically with GMP and the Community code relating to medicinal products for human use (Council Directive 2001/83/EC) has itself been the subject of substantial revision, via amending Directive 2004/27/EC, and these changes have been transposed into UK domestic legislation.

GMP Directive

The principles and guidelines of GMP are adopted by the European Commission under powers conferred by Council Directive 2001/83/EC. The objective of GMP is to ensure that products are consistently produced and controlled to particular quality standards.

Commission Directive 2003/94/EC (the "GMP Directive") sets out new requirements relating to the implementation of good manufacturing practice for medicinal products for human use (including Investigational Medicinal Products). The GMP Directive broadens the definition of good manufacturing practice set out in Directive 91/356/EEC and repealed the previous Directive in its entirety.

Changes to the Community Code

The amendments made by Directive 2004/27/EC in relation to manufacturing, wholesale dealing, supervision and sanctions are contained in Articles 1(32) to (39) and (55) to (60), (77) and (78). These provisions were implemented in the United Kingdom (along with some other miscellaneous "tidying-up" changes) by making regulations amending the relevant provisions of the Medicines Act 1968. The new arrangements came into force on 30 October 2005. The headline changes are as follows:

- New Community requirements[1] on pharmaceutical companies to adhere to the principles of GMP in the manufacturing processes of active substances used as starting materials. This includes any repackaging or relabelling activities carried out by a distributor or broker.
- New duty on QPs extending the need for full batch analysis and testing[2] (or re-testing) in a Member State to product imported from third countries (i.e. outside the Community), whether or not the product was originally manufactured in the Community.
- A new requirement[3] for distributors that import medicinal products from other Member States to notify the marketing authorisation holder and the competent authority of the Member State to which the product is imported of the intention to import.
- New powers[4] for the competent authority to carry out unannounced inspections at the premises of manufacturers of starting materials, or at the premises of marketing authorisation holders or any firms employed by the marketing authorisation holder where there are grounds for suspecting non-compliance with GMP principles.
- Changes to the system of licensing for third country imports. The importation of products from third countries now requires a manufacturing authorisation for import, rather than, as previously, a wholesale dealer's import licence.

UK legislation

New regulations[5] were introduced on 30 October 2005 to replace the Standard Provisions Regulations,[6] in relation to relevant medicinal products, i.e. medicinal products to which Directive 2001/83/EC as amended, apply. The previous Standard Provision Regulations, themselves, had

[1] Articles 1(33)–(35) of Directive 2004/27/EC amending Articles 46, 46a and 47 of Directive 2001/83/EC.

[2] Articles 1(36)–(38) of Directive 2004/27/EC amending Articles 49–50 of Directive 2001/83/EC.

[3] Article 1(55) of Directive 2004/27/EC amending Article 76 of Directive 2001/83/EC.

[4] Article 1(77) of Directive 2004/27/EC amending Article 111 of Directive 2001/83/EC.

[5] The Medicines for Human Use (Manufacturing, Wholesale Dealing and Miscellaneous Amendments) Regulations 2005 (SI 2005 No. 2789).

[6] The Medicines (Standard Provisions for Licences and Certificates) Regulations 1971 (SI 1971/972)

been amended nine times over the years. The Medicines for Human use (Manufacturing, Wholesale Dealing and Miscellaneous Amendments) Regulations 2005 match the amended European Directive requirements on medicines for human use.

Changes to the EU Guide to GMP

Following a restructuring of the GMP Guide publication, guidance on Basic Requirements for Active Substances used as Starting Materials (formerly Annex 18) now becomes the new Part II to the EC GMP Guide.

New/revised chapters

Chapter 1 has been revised to include new text on Product Quality Review, October 2005. A revised version, containing details of significant quality system-related responsibilities for monitoring, reporting, reviewing and trending requirements came into operation 1 January 2006.

Chapter 6 the revised version (October 2005) includes the on-going stability programme, which came into operation on 1 June 2006.

Chapter 8 was revised in December 2005 to include new requirements on counterfeit products, plus other minor modifications. The revised version came into operation on 1 February 2006.

New/revised annexes

Annex 1 (Manufacture of Sterile Medicinal Products): minor revisions made in September 2003.

Annex 13 (Manufacture of Investigational Medicinal Products): updated, with major revisions, July 2003.

Annex 19 (Reference and Retention Samples): a new annex, with detailed requirements, came into operation in June 2006.

Changes on the horizon

Two new sections are planned to the EC Guide to GMP. These relate to ICH Q9 and Q10, i.e. Quality Risk Management and Quality Systems. These may form new annexes to the Guide (Annexes 20 and 21, respectively) or they may form a separate part (Part III). Adoption is expected during 2007 or 2008.

In addition, further changes are expected during 2007 or 2008 relating to Chapter 4 and in respect of the following annexes: 2, 3, 6, 7, 11, 13 and 16.

The "*Orange Guide*" 2007

Many of the European Directives on medicinal products issued over the last thirty-five years were consolidated into two Directives during 2001, one for products used in humans and one for veterinary products. This makes the requirements more accessible. Although it is UK legislation, implementing the Directives, that bears directly on activities in the UK, it is often helpful for manufacturers and wholesalers to be aware of the original EU obligations. This is particularly so when trading across boundaries of Member States. Therefore, as before, the "Titles" or sections of Directive 2001/83/EC, as amended, dealing with manufacture and wholesale distribution of products for human use are included in this edition.

The UK's Code of Practice for Qualified Persons has been updated by the professional bodies in consultation with the MHRA; this is included.

Recommendations on meeting the important requirement to ensure the "proper conservation and distribution" of medicines requiring storage below ambient temperature ("cold-chain distribution") have been developed between representatives of wholesalers and the MHRA. These were published originally in the Pharmaceutical Journal,[7] were summarised in MAIL,[8] and are reproduced here in updated form.

Finally, there is a new section on the activities and services of the Inspection and Standards Division of the MHRA, which will be of interest to manufacturers and wholesalers.

Although much of the text in this book is available in its original form in other places, including various websites, we are pleased that the "Orange Guide" continues to satisfy a demand for information in one authoritative and convenient place. In particular, the detailed index to the Orange Guide adds value and simplifies the navigation of these complex documents. Readers are invited to suggest further updates to the Index, to the MHRA, for future improvements in navigation and cross-referencing.

For the 2007 version, we have, for the first time made the entire Orange Guide available online, as part of "MedicinesComplete" – a subscription-based database of leading medicines and healthcare references – and via CD-ROM. Also available is a separate GDP booklet for the wholesale dealing market. We hope that this new edition and the new formats will continue to be useful.

Gerald Heddell
Director, Inspection and Standards Division
December 2006

[7] Taylor J. Recommendations on the control and monitoring of storage and transportation temperatures of medicinal products. *Pharm J* 2001; 267: 128–131.

[8] MCA Newsletter MAIL, Issue 131, May/June 2002.

Acknowledgements

To the European Commission for permission to reproduce the text of the Directives, the EC Guide to GMP and the guidelines on Good Distribution Practice.

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Feedback

Comments on the content or presentation of the Orange Guide are encouraged and will be used to develop further editions. Your views are valued and both MHRA and Pharmaceutical Press would appreciate you taking the time to contact us. Please use the reply card enclosed with this edition or contact us directly by post, telephone, fax or email.

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Introduction

This publication brings together the main pharmaceutical regulations, directives and guidance which manufacturers and wholesalers are expected to follow when making and distributing medicinal products in the European Union and European Economic Area.[1] It is of particular relevance to all holders of manufacturer's licences and wholesale dealer's licences and to their Qualified Persons (QPs) and Responsible Persons (RPs), who have a responsibility for ensuring compliance with many of these regulatory requirements.

The obligation on governments of all Member States of the European Union to ensure that pharmaceutical manufacturers are authorised is stated in Title IV of Directive 2001/83/EC, as amended (products for human use) and of Directive 2001/82/EC (veterinary products). These titles, or sections, are also the source of requirements for compliance with Good Manufacturing Practice (GMP), employment of QPs and repeated inspections by the regulatory authorities. Title VII of the same Directive requires all wholesale distributors to be authorised, to have available RPs and comply with the guidelines on Good Distribution Practice (GDP).

The principles and guidelines of GMP are set out in two Commission Directives: 2003/94/EC for medicinal products for human use (replacing Directive 91/356/EEC) and 91/412/EEC for veterinary medicinal products. In the United Kingdom, the provisions for manufacturers and wholesale dealers have been implemented by requirements and undertakings incorporated in regulations[2] made under the Medicines Act 1968. Compliance with the principles and guidelines of GMP is a statutory requirement. The European Community (EC) Guide to GMP[3] (including its annexes)

[1] The member states of the European Community plus Iceland, Liechtenstein and Norway.

[2] The Medicines for Human Use (Manufacturing, Wholesale dealing and Miscellaneous Amendments) Regulations 2005 [S.I. 2005/2789].

[3] Commission of the European Communities. The rules governing medicinal products in the European Community. Vol IV. Good Manufacturing Practice for medicinal products.

provides detailed guidance which interprets and expands on the statutory principles and guidelines. Changes in technical knowledge and in regulations are reflected by additional and revised annexes.

GMP includes elements of the International Standard for Quality Management Systems ISO 9001:2000 with additional requirements specific to medicines. The UK first produced a national guide to GMP (known traditionally as the Orange Guide) in 1971. Guidance on good pharmaceutical wholesaling practice was added in the 1977 edition and a further edition was produced in 1983. The EC guidance, first issued for GMP in 1989 and for GDP in 1993, supersedes this and all other national guides of Member States, although much that was familiar in the old UK Guide can still be recognised in the EC guidance. The Pharmaceutical Inspection Co-operation Scheme has adopted the text of the EC Guide to GMP ensuring harmonisation of guidelines by its member inspectorates throughout the world. Mutual Recognition Agreements between the EC and several third countries have recognised the equivalence of GMP requirements of the parties concerned.

Manufacturers are required to name a QP on their manufacturer's licence. No batch of medicinal product may be released to the market within the EU unless a nominated QP has certified that it has been manufactured and checked in compliance with the laws in force. Guidance to QPs in fulfilling their responsibilities is given in the EC Guide to GMP and in the Code of Practice[4] for Qualified Persons which they are expected to follow. In similar spirit, wholesalers are required to appoint a RP who has the knowledge and responsibility to ensure that correct procedures are followed during distribution. Notes on the qualifications and duties of RPs are given to assist this.

The aim of GMP and GDP is to assure the quality of the medicinal product for the safety, well-being and protection of the patient. In achieving this aim it is impossible to over-emphasise the importance of people, at all levels, in the assurance of the quality of medicinal products. This is emphasised in the first principle in the EC Guide to GMP. The great majority of reported defective medicinal products has resulted from human error or carelessness, not from failures in technology. All the people involved with the production, Quality Control or distribution of medicinal products, whether key personnel, production or control or warehouse staff, inspectors of a regulatory authority or others involved in the many activities which lead to a patient taking a medicine, should bear this constantly in mind when performing their duties.

[4] The Institute of Biology, The Royal Pharmaceutical Society of Great Britain, The Royal Society of Chemistry. Code of Practice for Qualified Persons. In: Register of Qualified Persons. London: Institute of Biology, Royal Pharmaceutical Society of Great Britain, Royal Society of Chemistry, 2004.

SECTION

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MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY (MHRA)