The rules governing medicinal products
in the European Union

Volume 4

Good manufacturing practices

Medicinal products for human and veterinary use

1998 Edition

EUROPEAN COMMISSION
Directorate General III – Industry
Pharmaceuticals and cosmetics

THE RULES GOVERNING MEDICINAL PRODUCTS IN THE EUROPEAN UNION

Volume 1 Pharmaceutical legislation
Medicinal products for human use

Volume 2 Notice to applicants
Medicinal products for human use

Volume 3 Guidelines
Medicinal products for human use

Volume 4 Good manufacturing practices
Medicinal products for human and veterinary use

Volume 5 Pharmaceutical legislation
Veterinary medicinal products

Volume 6 Notice to applicants
Veterinary medicinal products

Volume 7 Guidelines
Veterinary medicinal products

Volume 8 Maximum residue limits
Veterinary medicinal products

Volume 9 Pharmacovigilance
Medicinal products for human and veterinary use

FOREWORD

The Pharmaceutical Industry of the European Community maintains high standards of Quality Assurance in the development, manufacture and control of medicinal products. A system of Marketing Authorisations ensures that all medicinal products are assessed by a Competent Authority to ensure compliance with contemporary requirements of safety, quality and efficacy. A system of Manufacturing Authorisations ensures that all products authorised on the European market are manufactured only by authorised manufacturers, whose activities are regularly inspected by the Competent Authorities. Manufacturing Authorisations are required by all pharmaceutical manufacturers in the European Community whether the products are sold within or outside of the Community.

Two directives laying down principles and guidelines of good manufacturing practice (GMP) for medicinal products were adopted by the Commission in 1991, the first for medicinal products for human use (Directive 91/356/EEC), the second one for veterinary use (Directive 91/412/EEC). Detailed guidelines in accordance with those principles are published in the Guide to Good Manufacturing Practice which will be used in assessing applications for Manufacturing authorisations and as a basis for inspection of manufacturers of medicinal products.

The principles of GMP and the detailed guidelines are applicable to all operations which require the authorisation referred to in Article 16 of Directive 75/319/EEC and in Article 24 of Directive 81/851/EEC as modified. They are also relevant for all other large scale pharmaceutical manufacturing processes, such as that undertaken in hospitals, and for the preparation of products for use in clinical trials.

All Member States and the Industry itself are agreed that the GMP requirements applicable to the manufacture of veterinary medicinal products are the same as those applicable to the manufacture of medicinal products for human use. Certain detailed adjustments to the GMP guidelines are set out in two annexes specific to veterinary medicinal products and to immunological veterinary medicinal products.

The Guide is presented in chapters, each headed by a principle. Chapter 1 on Quality Management outlines the fundamental concept of Quality Assurance as applied to the manufacture of medicinal products. Thereafter each chapter has a principle outlining the Quality Assurance objectives of that chapter and a text which provides sufficient detail for manufacturers to be made aware of the essential matters to be considered when implementing the principle.

In addition to the general matters of Good Manufacturing Practice outlined in the 9 chapters of this guide, a series of annexes providing detail about specific areas of activity is included. For some manufacturing processes, different annexes will apply simultaneously (e.g. annex on sterile preparations and on radiopharmaceuticals and/or on biological medicinal products).

A glossary of some terms used in the Guide has been incorporated after the annexes.

The first edition of the Guide was published in 1989, including an annex on the manufacture of sterile medicinal products.

The second edition was published in January 1992; including the Commission Directives 91/356 of 13 June 1991 and 91/412 of 23 July 1991 laying down the principles and guidelines on good manufacturing practice for medicinal products for human use as well as for veterinary medicinal products. The second edition also included 12 additional annexes.

The basic requirements in the main guide have not been modified. 14 annexes on the manufacture of medicinal products have been included in this third edition.

Annex 1 on the manufacture of sterile medicinal products has been modified. Annex 13 on the manufacture of investigational medicinal products, which was not included in the second edition of the Guide, has been modified and included in this version. Annex 14 on the manufacture of products derived from human blood or human plasma, which was not included in the second edition of the Guide, has been included in this version and a revision is scheduled for 1998.

The Guide is not intended to cover security aspects for the personnel engaged in manufacture. This may be particularly important in the manufacture of certain medicinal products such as highly active, biological and radioactive medicinal products, but they are governed by other provisions of Community or national law.

Throughout the Guide it is assumed that the requirements of the Marketing Authorisation relating to the safety, quality and efficacy of the products, are systematically incorporated into all the manufacturing, control and release for sale arrangements of the holder of the Manufacturing Authorisation.

The manufacture of medicinal products has for many years taken place in accordance with guidelines for Good Manufacturing Practice and the manufacture of medicinal products is not governed by CEN/ISO standards. Harmonised standards as adopted by the European standardisation organisations CEN/ISO may be used at industry's discretion as a tool for implementing a quality system in the pharmaceutical sector. The CEN/ISO standards have been considered but the terminology of these standards has not been implemented in this third edition of the Guide.

It is recognised that there are acceptable methods, other than those described in the Guide, which are capable of achieving the principles of Quality Assurance. The Guide is not intended to place any restraint upon the development of any new concepts or new technologies which have been validated and which provide a level of Quality Assurance at least equivalent to those set out in this Guide.

It will be regularly revised.

TABLE OF CONTENTS