

Introduction

The quality of pharmaceuticals has been a concern of the World Health Organization (WHO) since its inception. The setting of global standards is requested in Article 2 of the WHO Constitution, which cites as one of the Organization's functions that it should "develop, establish and promote international standards with respect to food, biological, pharmaceutical and similar products."

Every government allocates a substantial proportion of its total health budget to drugs. This proportion tends to be greatest in developing countries, where it may exceed 40%.

Without assurance that these drugs are relevant to priority health needs and that they meet acceptable standards of quality, safety and efficacy, any health service is evidently compromised. In developing countries considerable administrative and technical effort is directed to ensuring that patients receive effective drugs of good quality. It is crucial to the objective of health for all that a reliable system of drug control be brought within the reach of every country.

The supply of essential drugs of good quality was identified as one of the prerequisites for the delivery of health care at the International Conference on Primary Health Care in Alma-Ata in 1978. Similarly, the Conference of Experts on the Rational Use of Drugs, held in Nairobi in 1985, and WHO's Revised Drug Strategy, adopted by the World Health Assembly in May 1986, identified the effective functioning of national drug regulation and control systems as the only means to assure safety and quality of medicines. Yet the World Health Assembly continues to express great concern about the quality, safety and efficacy of medicines, particularly those products or active pharmaceutical substances imported into, or produced in, developing countries. In recent years counterfeit products have infiltrated certain markets in disquieting proportions. Since the founding of WHO, the World Health Assembly has adopted many resolutions requesting the Organization to develop international standards, recommendations and instruments to assure the quality of medicines, whether produced and traded nationally or internationally.

In response to these resolutions, the WHO Expert Committee on Specifications for Pharmaceutical Preparations, which was originally created to prepare *The international pharmacopoeia*, has made numerous recommendations relevant to quality assurance and control. Most of these recommendations, even

if they were made several years ago, are still valid. Thus far, however, most have been available only as separate sets of recommendations contained in annexes to various WHO Technical Reports. The recommendations are essential to all concerned with the quality assurance of medicines, but separate publication over a period of years made it difficult to recognize them as complementary parts of a comprehensive system of quality assurance.

To provide easy access to this information, the appropriate annexes are reproduced in the two volumes of this publication. They are supplemented with other material relevant to the quality assurance of pharmaceuticals, some already issued in the form of WHO documents. The information is not necessarily presented in chronological order of original issue. Instead it is presented in logical sequence as a series of administrative instruments and technical elements of an overall quality assurance system. Readers should bear in mind that, in certain previously published texts, reference is made to WHO guidelines and other documents that have since been updated. Some of these updated texts are themselves included in the compendium.

Volume 1 of *Quality assurance of pharmaceuticals: a compendium of guidelines and related materials* was published by WHO in 1997. Material relating to national drug regulations, product assessment and registration, *The international pharmacopoeia* and related activities, quality control laboratories, international trade in pharmaceuticals and their distribution, counterfeit products, basic tests for pharmaceutical products and training of technical personnel is collected and reproduced in Volume 1. Volume 2, published by WHO in 1999, reproduces guidelines related to good manufacturing practices (GMP) and to the inspection of pharmaceutical manufacturers and drug distribution channels. This updated edition of Volume 2 includes new texts and revisions.

Both for manufacturers and at national level, GMP are an important part of a comprehensive system of quality assurance. They also represent the technical standard upon which is based the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. The first GMP text published by WHO was developed during 1967–69 and revised in 1975. In the 1980s and early 1990s, several national and regional drug regulatory authorities issued or revised guidelines reflecting the ongoing elaboration of the concept of GMP. In addition, the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce was extended in 1988. Together, these developments necessitated an update of the existing guidelines on GMP published by WHO.

Revised and expanded GMP guidelines were prepared during 1989–90, approved by the WHO Expert Committee on Specifications for Pharmaceutical Preparations in late 1990 and published by WHO in 1992–2003. Part One of these revised and expanded guidelines sets out the philosophy and essential elements of GMP; Part Two deals with good practices in production and quality control. These two parts together represent the “core” of the GMP guidelines published by WHO.

Their provisions are fully consonant with those of other internationally recognized texts on GMP. GMP guidelines published by WHO are to be regarded as advisory in nature and may need to be adapted to address specific conditions in individual countries. However, if any departures from recommended practices are introduced, the equivalence of such alternative approaches should be validated.

In 1996, GMP guidelines were published by WHO for the validation of manufacturing processes. These guidelines were prepared to explain and promote the concept of validation embedded in the core GMP texts, and to assist in establishing priorities and selecting approaches when a validation programme is being developed. In 1997, the WHO Expert Committee on Specifications for Pharmaceutical Preparations approved an explanatory text on the role and functions of the “authorized person” at manufacturing establishments in the drug industry. The core GMP guidelines define the authorized person as the person responsible for the release of batches of finished products for sale. The explanatory text is intended to assist manufacturers wishing to strengthen their quality assurance systems. These concepts have been integrated in its revised text.

The core GMP guidelines, along with those for the validation of manufacturing processes and the explanatory text on the role and functions of the authorized person, are reproduced in **Chapter 1** (Main principles for pharmaceutical products) in their updated form.

Part Three of the GMP guidelines published by WHO in 1992–2003 constituted in its update form the first instalment in an ongoing series of applications of the principles of GMP to various specialized areas. For instance, advice regarding GMP for active pharmaceutical ingredients appeared as section 18 in Part Three. This section, along with the GMP guidelines on the manufacture of pharmaceutical excipients, which were approved by the WHO Expert Committee on Specifications for Pharmaceutical Preparations in 1997, is reproduced in **Chapter 2** (Starting materials). These two texts constitute the existing body of GMP guidance for pharmaceutical starting materials. As strict application of full GMP is not always practical or necessary for such materials, these texts outline the procedures and practices that manufacturers should employ to ensure that the methods, facilities and controls used for their production are operated or managed so that pharmaceutical starting materials have the quality and purity appropriate for use in finished pharmaceutical products.

On the other hand, certain specific kinds of pharmaceutical products demand practices or procedures not described in the core GMP guidelines. For example, section 17 in Part Three of the 1992 guidelines, updated in 2002 stresses additional points necessary to minimize the risks of microbiological, particulate and pyrogen contamination in sterile pharmaceutical products. Other specialized GMP guidelines were subsequently published by WHO for biological products, investigational pharmaceutical products, herbal medicinal products, radiopharmaceuticals, etc.

The GMP guidelines for biological products have been approved by both the WHO Expert Committee on Biological Standardization (1991) and the WHO

Expert Committee on Specifications for Pharmaceutical Preparations (1992). Unlike conventional pharmaceutical products which are normally produced and controlled by means of reproducible chemical and physical techniques, biological products are manufactured with biological materials and processes, such as the cultivation of cells or the extraction of materials from living organisms. As such materials and processes display inherent variability, the range and nature of manufacturing by-products in biological products are likewise variable. For such products, including allergens, antigens, vaccines, hormones, cytokines, enzymes, human whole-blood and plasma derivatives, immune sera, immunoglobulins, products of fermentation and diagnostic agents for *in vitro* use, full adherence to the GMP guidelines for biological products is recommended for all production steps, including those from which active ingredients are produced.

The GMP guidelines for the manufacture of investigational pharmaceutical products for clinical trials in humans supplement both the core GMP guidelines for pharmaceutical products and “Guidelines for good clinical practice (GCP) for trials on pharmaceutical products” (WHO Technical Report Series, No. 850, 1995, pp. 97–137). These specialized GMP guidelines specifically address those manufacturing practices that may be different for investigational products (which are not usually manufactured in accordance with a set routine), and which may be incompletely characterized during the initial stages of clinical development.

The specialized GMP guidelines for the manufacture of herbal medicinal products address the manufacture of products from material of plant origin, which may be subject to contamination and deterioration and vary in its composition and properties. Furthermore, in the manufacture and quality control of herbal medicinal products, procedures and techniques are often used that are substantially different from those employed for conventional pharmaceutical products.

The text on *radiopharmaceuticals* has been developed in close collaboration with the International Atomic Energy Agency (IAEA). The text covers radiopharmaceutical products that are prepared in hospital radiopharmacies, centralized radiopharmacies, nuclear centres and institutes or by industrial manufacturers, as well as in positron emission tomography (PET) centres.

These five sets of specialized guidelines—for sterile, biological, investigational and herbal products and for radiopharmaceuticals—are reproduced in **Chapter 3** (Specific pharmaceutical products).

Inspection is closely related to other elements of the overall drug quality assurance system: GMP, licensing of manufacturing facilities, product registration, etc. Without a competent inspectorate operating to high professional standards, neither GMP compliance nor licensing provisions can be effectively enforced. In addition, inspection of manufacturing facilities is pivotal to the operation of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce, which provides for the issuance of an attestation that a given product is manufactured under GMP conditions as established by periodic inspections.

A text on *pre-approval inspections* was developed to complement the text on inspections, described below. These guidelines apply to the inspection of manufacturing and quality control facilities prior to the issuing of a marketing authorization for a pharmaceutical product.

A text entitled “Provisional guidelines on the inspection of pharmaceutical manufacturers” was published by WHO in 1992 along with the core GMP guidelines on pharmaceutical products. The provisional guidelines were intended to promote the harmonization of inspection practices among WHO Member States, and the Expert Committee noted that they would be of particular value to government inspectors operating within small national regulatory authorities.

In general, the objective of inspecting pharmaceutical manufacturing facilities is either to enforce general GMP compliance or to provide authorization for the manufacture of specific pharmaceutical products, usually in relation to an application for registration. The provisional guidelines are applicable mostly to inspections of the first type, whether performed before a manufacturing authorization is issued, or on a periodic, routine basis.

A further aspect of pharmaceutical inspection is monitoring the quality of pharmaceutical products in distribution channels, that is, from the point of manufacture to delivery to the recipient. In recent years the hazard posed by the infiltration of counterfeit products has been identified in addition to problems related to the inadequate stability of drug products and their improper handling and storage. The text “Guidelines for inspection of drug distribution channels”, part of the thirty-fifth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, is included in this volume and provides detailed advice to national drug regulatory authorities on the inspection of distribution channels.

The provisional guidelines on the inspection of pharmaceutical manufacturers and the guidelines for inspection of drug distribution channels are reproduced in **Chapter 4** (Inspections).

Recently, with the worldwide acceptance of the ISO 9000-series standards addressing quality management and quality systems, a trend has emerged in some Member States for non-commercial institutions such as certification bodies, testing laboratories and the like to introduce principles of quality systems into their internal operations. The same principles have begun to be applied to governmental pharmaceutical inspectorates and drug control laboratories. The WHO Expert Committee on Specifications for Pharmaceutical Preparations recently recommended that further guidance in this area should address the introduction of quality systems principles in the practice of pharmaceutical inspections.

Additional guidance is also currently being developed to cover inspections of manufacturing and quality control facilities conducted before a marketing authorization (i.e. product licence or registration) for a pharmaceutical product is granted.

Following the publication of the guidance texts on inspections, additional

guidelines dealing with the *quality system requirements for national good manufacturing practice inspectorates* were adopted by the Expert Committee. This guidance is one important tool when implementing GMP. The establishment and operation of a quality system is an essential element in the mutual recognition among inspectorates. The quality system should include all activities involved in the inspection.

To complement the set of guidance texts in this area, the Expert Committee adopted a model layout for an *inspection report*, as well as a *model certificate of GMP for a manufacturing site*.

Hazards affecting quality are to a certain extent covered and controlled through the validation of critical operations and processes in the manufacture of finished pharmaceutical products in accordance with GMP. However, GMP do not cover the safety of the personnel engaged in manufacture, whereas the application of hazard analysis and critical control point (HACCP) methodology does. Traditionally, this concept has been applied to food safety management systems. The same principles have increasingly also been adopted in other industries. The new guidance reproduced in this volume, in **Chapter 5** (Hazard and risks analysis in pharmaceutical products), suggests their use also in the area of pharmaceuticals.

An alphabetical index of subjects covered in Volumes 1 and 2 of *Quality assurance of pharmaceuticals: a compendium of guidelines and related materials* is included at the end of this volume.