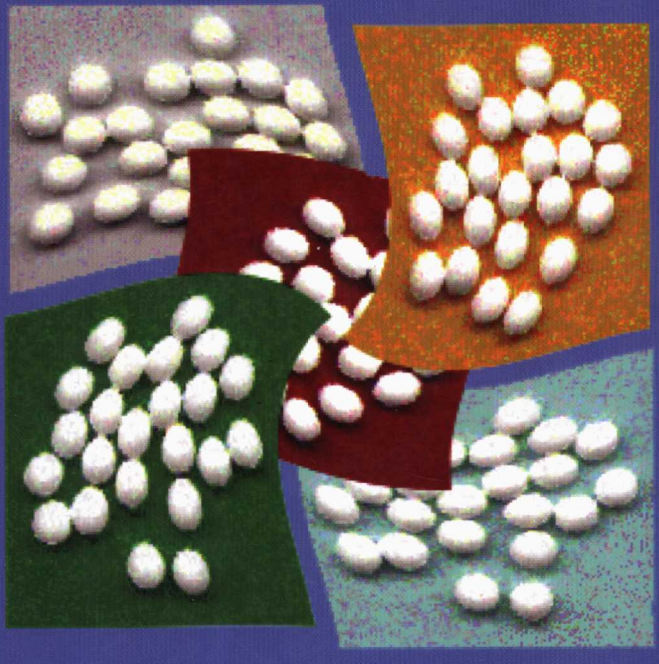
Quality assurance of pharmaceuticals

A compendium of guidelines and related materials

Volume 2

Good manufacturing practices and inspection



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The World Health Organization was established in 1948 as a specialized agency of the United Nations serving as the directing and coordinating authority for international health matters and public health. One of WHO's constitutional functions is to provide objective and reliable information and advice in the field of human health, a responsibility that it fulfils in part through its extensive programme of publications.

The Organization seeks through its publications to support national health strategies and address the most pressing public health concerns of populations around the world. To respond to the needs of Member States at all levels of development, WHO publishes practical manuals, handbooks and training material for specific categories of health workers; internationally applicable guidelines and standards; reviews and analyses of health policies, programmes and research; and state-of-the-art consensus reports that offer technical advice and recommendations for decision-makers. These books are closely tied to the Organization's priority activities, encompassing disease prevention and control, the development of equitable health systems based on primary health care, and health promotion for individuals and communities. Progress towards better health for all also demands the global dissemination and exchange of information that draws on the knowledge and experience of all WHO's Member countries and the collaboration of world leaders in public health and the biomedical sciences.

To ensure the widest possible availability of authoritative information and guidance on health matters, WHO secures the broad international distribution of its publications and encourages their translation and adaptation. By helping to promote and protect health and prevent and control disease throughout the world, WHO's books contribute to achieving the Organization's principal objective – the attainment by all people of the highest possible level of health.

Contents

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. This second volume reproduces guidelines related to good manufacturing practices (GMP) and to the inspection of pharmaceutical manufacturers and drug distribution channels.

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. 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.

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

Part Three of the GMP guidelines published by WHO in 1992 constituted 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 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 and herbal medicinal products.

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 on good clinical practice 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.

These four sets of specialized guidelines—for sterile, biological, investigational and herbal products—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 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 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 for the inspection of manufacturers and the guidelines for inspection of distribution channels are reproduced in **Chapter 4** (Inspection).

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.

It is anticipated that further GMP guidelines will be published by WHO. Revision of the GMP texts on sterile pharmaceutical products and active pharmaceutical ingredients (sections 17 and 18 in Part Three of the GMP guidelines for pharmaceutical products) is already under consideration.

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.

1.

WHO good manufacturing practices: main principles for pharmaceutical products

Introductory note, general considerations and glossary[1,2]

Introductory note

The first World Health Organization (WHO) draft text on good manufacturing practices (GMP) was prepared at the request of the Twentieth World Health Assembly (resolution WHA20.34) in 1967 by a group of consultants. It was subsequently submitted to the Twenty-first World Health Assembly under the title "Draft requirements for good manufacturing practice in the manufacture and quality control of drugs and pharmaceutical specialities" and was accepted.

The revised text was discussed by the WHO Expert Committee on Specifications for Pharmaceutical Preparations in 1968 and published as an annex to its twenty-second report (*1*). The text was further reproduced (with some revisions) in 1971 in the Supplement to the second edition of *The international pharmacopoeia*.

When the World Health Assembly recommended the first version of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce in resolution WHA22.50 (1969), it accepted at the same time the GMP text as an integral part of the Scheme. The revised versions of both the Certification Scheme and the GMP text were adopted in resolution WHA28.65 in 1975. Since then, the Certification Scheme has been extended to include certification of:

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[1] Taken from: Good manufacturing practices for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second Report.* Geneva, World Health Organization, 1992: 16–22 (WHO Technical Report Series, No. 823).

[2] Parts One, Two and Three of Good manufacturing practices for pharmaceutical products are reproduced elsewhere in this volume (see pp. 13–45, 46–53, 75–83, 103–117).

— veterinary products administered to food-producing animals;
— starting materials for use in dosage forms, when they are subject to control by legislation in the exporting Member State and in the importing Member State; and
— information on safety and efficacy (resolution WHA41.18, 1988).

The GMP text, however, has not been revised since 1975.

Considerable developments have occurred in GMP in the intervening years, and important national and international documents including new revisions have appeared, such as:

— *Guide to good pharmaceutical manufacturing practice 1983*. London, Her Majesty's Stationery Office, 1983 ("Orange Guide"). [Superseded by the 1992 EEC guide.]
— *Bonnes pratiques de fabrication et de production pharmaceutiques*. Paris, Ministère des Affaires Sociales et de la Solidarité Nationale, Secrétariat d'Etat chargé de la Santé, Direction de la Pharmacie et du Médicament, 1985. [Superseded by the 1992 EEC guide.]
— *ASEAN good manufacturing practices guidelines*, 2nd ed. Association of South East Asian Nations, 1988.
— *Good manufacturing practice for medicinal products in the European Community*. Commission of the European Communities, 1992.
— *Guide to good manufacturing practice for pharmaceutical products*. Convention for the Mutual Recognition of Inspection in Respect of the Manufacture of Pharmaceutical Products (PIC), 1992.

New types of guidelines have appeared in recent years: GMP texts applicable to the manufacture of bulk pharmaceutical chemicals as opposed to the manufacture of formulations of dosage forms (PIC guidelines, 1987; various national documents). Another important development in the industry at large is the appearance of the guidelines of the International Organization for Standardization (ISO), specifically the ISO 9000 to 9004 standards for quality systems (1987 rev. 1990). These developments, together with plans to expand and revise the Certification Scheme call for the revision of the WHO GMP text.

The revised draft requirements for GMP are presented in three parts. Part One, "Quality management in the drug industry: philosophy and essential elements", outlines the general concepts of quality assurance as well as the principal components or subsystems of GMP, which are joint responsibilities of the top management and of production and quality control management. These include hygiene, validation, self-inspection, personnel, premises, equipment, materials, and documentation.

Part Two, "Good practices in production and quality control", provides guidance on actions to be taken separately by production and by quality control personnel for the implementation of the general principles of quality assurance.

Part Three contains two supplementary guidelines, but it is an open-ended section, and it is anticipated that further guidelines will be developed in the future, e.g., for biological products, materials for clinical trials, and validation.

The provisions in this guide are fully consonant with those in the above-mentioned documents published by the EEC and PIC.

General considerations

Licensed pharmaceutical products should be manufactured only by licensed manufacturers (holders of a manufacturing authorization) whose activities are regularly inspected by competent national authorities. This guide to GMP shall be used as a standard to justify GMP status, which constitutes one of the elements of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce, through the assessment of applications for manufacturing authorizations and as a basis for the inspection of manufacturing facilities. It may also be used as training material for government drug inspectors, as well as for production and quality control personnel in the industry.

The guide is applicable to all large-scale operations for the production of drugs in their finished dosage forms, including large-scale processes in hospitals and the preparation of clinical trials supplies.

The good practices outlined below are to be considered general guides,[1] and they may be adapted to meet individual needs. The equivalence of alternative approaches to quality assurance should be validated. Parts One and Two of this guide are not intended to cover the production of active pharmaceutical ingredients for which specific requirements are presented in section 18. Nor does the guide as a whole cover safety aspects for the personnel engaged in manufacture: those are governed by national legislation. However, the manufacturer must assure the safety of workers. Nonproprietary names for pharmaceutical substances designated by WHO should be used when available, together with other designated names.

Glossary

The definitions given below apply to the terms used in this guide. They may have different meanings in other contexts.

active pharmaceutical ingredient
A substance or compound that is intended to be used in the manufacture of a pharmaceutical product as a pharmacologically active compound (ingredient).

[1] The word "should" in the text means a strong recommendation.

airlock
An enclosed space with two or more doors, which is interposed between two or more rooms, e.g., of differing classes of cleanliness, for the purpose of controlling the airflow between those rooms when they need to be entered. An airlock is designed for and used by either people or goods.

authorized person
A person responsible for the release of batches of finished product for sale. In certain countries the batch documentation of a batch of finished product must be signed by an authorized person from the production department and the batch test results by an authorized person from the quality control department for batch release.

batch (or lot)
A defined quantity of starting material, packaging material, or product processed in a single process or series of processes so that it could be expected to be homogeneous. In the case of continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch.

batch number (or lot number)
A distinctive combination of numbers and/or letters which specifically identifies a batch on the labels, the batch records, the certificates of analysis, etc.

batch numbering system
Standard operating procedure describing the details of the batch numbering.

batch records
All documents associated with the manufacture of a batch of bulk product or finished product. They provide a history of each batch of product and of all circumstances pertinent to the quality of the final product.

bulk product
Any product that has completed all processing stages up to, but not including, final packaging.

calibration
The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), recording, and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established.

clean area
An area with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation, and retention of contaminants within the area.

consignment (or delivery)
The quantity of starting material, or of a drug product, made by one manufacturer and supplied at one time in response to a particular request or order. A consignment may comprise one or more packages or containers and may include material belonging to more than one batch.

critical process
A process that may cause variation in the quality of the pharmaceutical product.

cross-contamination
Contamination of a starting material, intermediate product, or finished product with another starting material or product during production.

finished product
A product that has undergone all stages of production, including packaging in its final container and labelling.

in-process control
Checks performed during production in order to monitor and if necessary to adjust the process to ensure that the product conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control.

intermediate product
Partly processed material that must undergo further manufacturing steps before it becomes a bulk product.

large-volume parenterals
Sterile solutions intended for parenteral application with a volume of 100 ml or more in one container of the finished dosage form.

manufacture
All operations of purchase of materials and products, production, quality control, release, storage, shipment of finished products, and the related controls.

manufacturer
A company that carries out at least one step of manufacture.

marketing authorization (product licence, registration certificate)
A legal document issued by the competent drug regulatory authority that establishes the detailed composition and formulation of the product and the pharmacopoeial or other recognized specifications of its ingredients and of the final product itself, and includes details of packaging, labelling, and shelf-life.

master formula
A document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls.

master record
A document or set of documents that serve as a basis for the batch documentation (blank batch record).

packaging
All operations, including filling and labelling, that a bulk product has to undergo in order to become a finished product. Sterile filling would not normally be regarded as part of packaging, the bulk product being the filled, but not the finally packaged, primary container.

packaging material
Any material, including printed material, employed in the packaging of a pharmaceutical product, excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

pharmaceutical product
Any medicine intended for human use or veterinary product administered to food-producing animals, presented in its finished dosage form or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in both the exporting state and the importing state.

processing instructions
See master formula.

production
All operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing and packaging, to completion of the finished product.

quality assurance
See Part One (pp. 13–45).

quality control
See Part One (pp. 13–45).

quarantine
The status of starting or packaging materials, intermediates, or bulk or finished products isolated physically or by other effective means while a decision is awaited on their release, rejection, or reprocessing.

reconciliation
A comparison, making due allowance for normal variation, between the amount of product or materials theoretically produced or used and the amount actually produced or used.

recovery (or blending)
The introduction of all or part of previous batches (or of redistilled solvents and similar products) of the required quality into another batch at a defined stage of manufacture.

reprocessing
The reworking of all or part of a batch of product of an unacceptable quality from a defined stage of production so that its quality may be rendered acceptable by one or more additional operations.

returned product
Finished product sent back to the manufacturer.

specification
A document describing in detail the requirements with which the products or materials used or obtained during manufacture have to conform. Specifications serve as a basis for quality evaluation.

standard operating procedure (SOP)
An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material but of a more general nature (e.g., equipment operation, maintenance and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

starting material
Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials.