



# Quality assurance of pharmaceuticals

A compendium of  
guidelines and related materials

**Volume 2, Updated edition**

Good manufacturing practices  
and inspection



World Health Organization  
Geneva



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.



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and request a copy of our **catalogue of WHO Information products on pharmaceuticals** at the above address.



Assurance of the quality, safety and efficacy of pharmaceutical products is a continuing concern of WHO. Despite efforts made around the world to ensure a supply of high-quality and effective drugs, substandard, spurious and counterfeit products still compromise health care delivery in many countries.

To respond to the global need for adequate quality assurance of pharmaceuticals, WHO's Expert Committee on Specifications for Pharmaceutical Preparations has over the years made numerous recommendations to establish standards and guidelines and to promote the effective functioning of national regulation and control systems and the implementation of internationally agreed standards by trained personnel. Many of the relevant documents endorsed by the Committee are reproduced in this volume, providing guidance covering all aspects of good manufacturing practices. Important texts on inspection are also included.

Most of the material has been published separately in the Expert Committee's reports. This compendium brings it together for the first time to make it more accessible and of greater practical value to those working in faculties of pharmacy, in drug regulation and control, and in the pharmaceutical industry.

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***Volume 2***  
***Updated edition***

Good manufacturing practices and inspection





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# Contents

<b>Introduction</b>	1
<b>1. WHO good manufacturing practices: main principles for pharmaceutical products</b>	7
Quality management in the drug industry: philosophy and essential elements	15
<b>2. WHO good manufacturing practices: starting materials</b>	58
Active pharmaceutical ingredients (bulk drug substances)	58
Pharmaceutical excipients	66
<b>3. WHO good manufacturing practices: specific pharmaceutical products</b>	86
Sterile pharmaceutical products	86
Biological products	103
Investigational pharmaceutical products for clinical trials in humans	113
Herbal medicinal products	125
Radiopharmaceutical products	130
<b>4. Inspection</b>	139
Pre-approval inspections	139
Inspection of pharmaceutical manufacturers	145
Inspection of drug distribution channels	157
Quality systems requirements for national good manufacturing practice inspectorates	176
Guidance on good manufacturing practices: inspection report	193
Model certificate of good manufacturing practices	197
<b>5. Hazard and risk analysis in pharmaceutical products</b>	200
Application of hazard analysis and critical control point (HACCP) methodology to pharmaceuticals	200
<b>Index</b>	213





# 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



## QUALITY ASSURANCE OF PHARMACEUTICALS

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. New texts and revisions are included in this volume.

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. In following reports 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 authorized person, are reproduced in **Chapter 1** (Main principles for pharmaceutical products).

Part Three of the GMP guidelines published by WHO in 1992 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 stresses additional points necessary to minimize the risks of microbiological, particulate and pyrogen contamination in sterile pharmaceutical products and updated in 2002. 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 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.

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, in vestigational, herbal products and 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 the *pre-approved of inspections* was developed to complement the text on inspections, described thereafter. These guidelines are offered when inspecting 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 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.

Following the publication of the guidance texts on inspections, additional



## QUALITY ASSURANCE OF PHARMACEUTICALS

guidelines were adopted by the Expert Committee dealing with *the quality system requirements for national good manufacturing practice inspectorates*. 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 in this area, the Expert Committee adopted a model lay-out 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 the 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 suggested its use also to 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.





# 1.

## WHO good manufacturing practices: main principles for pharmaceutical products<sup>1</sup>

Introduction	8
General considerations	9
Glossary	9
Quality management in the drug industry: philosophy and essential elements	15
1. Quality assurance	16
2. Good manufacturing practices for pharmaceutical products (GMP)	17
3. Sanitation and hygiene	18
4. Qualification and validation	18
5. Complaints	29
6. Product recalls	20
7. Contract production and analysis	21
General	21
The contract giver	21
The contract acceptor	22
The contract	22
8. Self-inspection and quality audits	23
Items for self-inspection	24
Self-inspection team	24
Frequency of self-inspection	24
Self-inspection report	24
Follow-up action	24
Quality audit	25
Suppliers' audits and approval	25
9. Personnel	25
General	25
Key personnel	26
10. Training	28
11. Personal hygiene	29
12. Premises	30
General	30
Ancillary areas	31

<sup>1</sup> Ref.: WHO Technical Report Series, No. 908, 2003 (Annex 4), pp. 37–89



## QUALITY ASSURANCE OF PHARMACEUTICALS

Storage areas	31
Weighing areas	32
Production areas	32
Quality control areas	33
13. Equipment	34
14. Materials	35
General	35
Starting materials	35
Packaging materials	36
Intermediate and bulk products	37
Finished products	37
Rejected, recovered, reprocessed and reworked materials	37
Recalled products	38
Returned goods	38
Reagents and culture media	38
Reference standards	39
Waste materials	39
Miscellaneous	39
15. Documentation	40
General	40
Documents required	41
16. Good practices in production	48
General	48
Prevention of cross-contamination and bacterial contamination during production	49
Processing operations	50
Packaging operations	51
17. Good practices in quality control	52
Control of starting materials and intermediate, bulk and finished products	54
Test requirements	55
Batch record review	56
Stability studies	56
References	57

### Introduction

The first WHO draft text on good manufacturing practices (GMP) was prepared in 1967 by a group of consultants at the request of the Twentieth World Health Assembly (resolution WHA20.34). 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. The text was then reproduced (with some revisions) in 1971 in the Supplement to the second edition of *The International Pharmacopoeia*.

In 1969, 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, it accepted at the same time the GMP text as an integral part of the Scheme. Revised versions of both the Certification Scheme and the GMP text were adopted in 1975 by resolution WHA28.65. Since then, the Certification Scheme has been extended to include the certification of:

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

In 1992, the revised draft requirements for GMP were presented in three parts, of which only Parts One and Two are reproduced in this document (1).

“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 top management and of production and quality control management. These include hygiene, validation, self-inspection, personnel, premises, equipment, materials and documentation.

“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.

These two parts were subsequently supplemented by further guidelines which are integral parts of these good manufacturing practices for pharmaceutical products. All these texts are available on the web page of the World Health Organization. (<http://www.who.int/medicines/organization/qsm/activities/qualityassurance/gmp/gmpcover.html>) Considerable developments in GMP have taken place in the intervening years, and important national and international documents, including new revisions, have appeared (2, 3, 4, 5). Thus the necessity to revise the main principles and incorporate the concept of validation.

## General considerations

Licensed pharmaceutical products (marketing authorization) 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 Pharma-



## QUALITY ASSURANCE OF PHARMACEUTICALS

ceutical 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, quality control and quality assurance personnel in the industry.

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

The good practices outlined below are to be considered general guides<sup>1</sup>, and they may be adapted to meet individual needs. The equivalence of alternative approaches to quality assurance, however, should be validated. The guide as a whole does not cover safety aspects for the personnel engaged in manufacture or environmental protection: these are normally governed by national legislation. A new concept of hazard analysis related to the risks in production and personnel safety is also newly recommended (Annex 7). The manufacturer should assure the safety of workers and take the necessary measures to prevent pollution of the external environment. International Nonproprietary Names (INNs) 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 (API)*

Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

#### *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 use either by people or for goods and/or equipment.

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<sup>1</sup> The word "should" in the text means a strong recommendation.



## MAIN PRINCIPLES FOR PHARMACEUTICAL PRODUCTS

### *authorized person*

The person recognized by the national regulatory authority as having the responsibility for ensuring that each batch of finished product has been manufactured, tested and approved for release in compliance with the laws and regulations in force in that country.

### *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 is expected to be homogeneous. 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. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

### *batch number (or lot number)*

A distinctive combination of numbers and/or letters which uniquely identifies a batch on the labels, its batch records and corresponding certificates of analysis, etc.

### *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.



## QUALITY ASSURANCE OF PHARMACEUTICALS

### *consignment (or delivery)*

The quantity of a pharmaceutical(s), 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.

### *contamination*

The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or on to a starting material or intermediate during production, sampling, packaging or repackaging, storage or transport.

### *critical operation*

An operation in the manufacturing 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 finished dosage form that has undergone all stages of manufacture, 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 product 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 and distribution of pharmaceutical products, and the related controls.



*manufacturer*

A company that carries out operations such as production, packaging, repackaging, labelling and relabelling of pharmaceuticals.

*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. Filling of a sterile product under aseptic conditions or a product intended to be terminally sterilized, would not normally be regarded as part of packaging.

*packaging material*

Any material, including printed material, employed in the packaging of a pharmaceutical, but 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 material or product intended for human or veterinary use 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 the exporting state and/or the importing state.

*production*

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



## QUALITY ASSURANCE OF PHARMACEUTICALS

### *qualification*

Action of proving that any premises, systems and items of equipment work correctly and actually lead to the expected results. The meaning of the word “validation” is sometimes extended to incorporate the concept of qualification.

### *quality assurance*

See Part One (pp. 7–35).

### *quality control*

See Part One (pp. 7–35).

### *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 between the theoretical quantity and the actual quantity.

### *recovery*

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. It includes the removal of impurities from waste to obtain a pure substance or the recovery of used materials for a separate use.

### *reprocessing*

Subjecting all or part of a batch or lot of an in-process drug, bulk process intermediate (final biological bulk intermediate) or bulk product of a single batch/lot to a previous step in the validated manufacturing process due to failure to meet predetermined specifications. Reprocessing procedures are foreseen as occasionally necessary for biological drugs and, in such cases, are validated and pre-approved as part of the marketing authorization.

### *reworking*

Subjecting an in-process or bulk process intermediate (final biological bulk intermediate) or final product of a single batch to an alternate manufacturing process due to a failure to meet predetermined specifications. Reworking is an unexpected occurrence and is not pre-approved as part of the marketing authorization.

### *self-contained area*

Premises which provide complete and total separation of all aspects of an operation, including personnel and equipment movement, with well established procedures, controls and monitoring. This includes physical barriers as well as separate





## MAIN PRINCIPLES FOR PHARMACEUTICAL PRODUCTS

air-handling systems, but does not necessarily imply two distinct and separate buildings.

### *specification*

A list of detailed requirements with which the products or materials used or obtained during manufacture have to conform. They 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 (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.

### *validation*

Action of proving, in accordance with the principles of GMP, that any procedure, process, equipment, material, activity or system actually leads to the expected results (see also qualification).

## Quality management in the drug industry: philosophy and essential elements<sup>1</sup>

In the drug industry at large, quality management is usually defined as the aspect of management function that determines and implements the “quality policy”, i.e. the overall intention and direction of an organization regarding quality, as formally expressed and authorized by top management.

The basic elements of quality management are:

- an appropriate infrastructure or “quality system”, encompassing the organizational structure, procedures, processes and resources;
- systematic actions necessary to ensure adequate confidence that a product (or service) will satisfy given requirements for quality. The totality of these actions is termed “quality assurance”.

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<sup>1</sup> Good manufacturing practices for pharmaceutical products, Part One. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report*. Geneva, World Health Organization, 1992, Annex 1 (WHO Technical Report Series, No. 823).



## QUALITY ASSURANCE OF PHARMACEUTICALS

Within an organization, quality assurance serves as a management tool. In contractual situations, quality assurance also serves to generate confidence in the supplier.

The concepts of quality assurance, GMP and quality control are interrelated aspects of quality management. They are described here in order to emphasize their relationship and their fundamental importance to the production and control of pharmaceutical products.

### 1. Quality assurance

1.1 *Principle.* “Quality assurance” is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use. Quality assurance therefore incorporates GMP and other factors, including those outside the scope of this guide such as product design and development.

1.2 The system of quality assurance appropriate to the manufacture of pharmaceutical products should ensure that:

- (a) pharmaceutical products are designed and developed in a way that takes account of the requirements of GMP and other associated codes such as those of good laboratory practice (GLP)<sup>1</sup> and good clinical practice (GCP);
- (b) production and control operations are clearly specified in a written form and GMP requirements are adopted;
- (c) managerial responsibilities are clearly specified in job descriptions;
- (d) arrangements are made for the manufacture, supply and use of the correct starting and packaging materials;
- (e) all necessary controls on starting materials, intermediate products, and bulk products and other in-process controls, calibrations, and validations are carried out;
- (f) the finished product is correctly processed and checked, according to the defined procedures;
- (g) pharmaceutical products are not sold or supplied before the authorized persons (see also sections 9.11 & 9.12) have certified that each production batch has been produced and controlled in accordance with the requirements of the marketing authorization and any other regulations

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<sup>1</sup> This is a code governing the testing of chemicals to obtain data on their properties and ensuring safety with respect to human health and the environment. It is different from that described in “Good laboratory practices in governmental drug control laboratories” in the Thirtieth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (WHO Technical Report Series, No. 748, 1987, Annex 1).



## MAIN PRINCIPLES FOR PHARMACEUTICAL PRODUCTS

- relevant to the production, control and release of pharmaceutical products;
- (h) satisfactory arrangements exist to ensure, as far as possible, that the pharmaceutical products are stored by the manufacturer, distributed, and subsequently handled so that quality is maintained throughout their shelf-life;
  - (i) there is a procedure for self-inspection and/or quality audit that regularly appraises the effectiveness and applicability of the quality assurance system;
  - (j) deviations are reported, investigated and recorded;
  - (k) there is a system for approving changes that may have an impact on product quality;
  - (l) regular evaluations of the quality of pharmaceutical products should be conducted with the objective of verifying the consistency of the process and ensuring its continuous improvement.

1.3 The manufacturer must assume responsibility for the quality of the pharmaceutical products to ensure that they are fit for their intended use, comply with the requirements of the marketing authorization and do not place patients at risk due to inadequate safety, quality or efficacy. The attainment of this quality objective is the responsibility of senior management and requires the participation and commitment of staff in many different departments and at all levels within the company, the company's suppliers, and the distributors. To achieve the quality objective reliably there must be a comprehensively designed and correctly implemented system of quality assurance incorporating GMP and quality control. It should be fully documented and its effectiveness monitored. All parts of the quality assurance system should be adequately staffed with competent personnel, and should have suitable and sufficient premises, equipment, and facilities.

## 2. Good manufacturing practices for pharmaceutical products (GMP)

2.1 Good manufacturing practice is that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization. GMP are aimed primarily at diminishing the risks inherent in any pharmaceutical production. Such risks are essentially of two types: cross-contamination (in particular of unexpected contaminants) and mix-ups (confusion) caused by, for example, false labels being put on containers. Under GMP:

- (a) all manufacturing processes are clearly defined, systematically reviewed in the light of experience, and shown to be capable of consistently manufacturing pharmaceutical products of the required quality that comply with their specifications;
- (b) qualification and validation are performed;



## QUALITY ASSURANCE OF PHARMACEUTICALS

- (c) all necessary resources are provided, including:
  - (i) appropriately qualified and trained personnel;
  - (ii) adequate premises and space;
  - (iii) suitable equipment and services;
  - (iv) appropriate materials, containers and labels;
  - (v) approved procedures and instructions;
  - (vi) suitable storage and transport;
  - (vii) adequate personnel, laboratories and equipment for in-process controls;
- (d) instructions and procedures are written in clear and unambiguous language, specifically applicable to the facilities provided;
- (e) operators are trained to carry out procedures correctly;
- (f) records are made (manually and/or by recording instruments) during manufacture to show that all the steps required by the defined procedures and instructions have in fact been taken and that the quantity and quality of the product are as expected; any significant deviations are fully recorded and investigated;
- (g) records covering manufacture and distribution, which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form;
- (h) the proper storage and distribution of the products minimizes any risk to their quality;
- (i) a system is available to recall any batch of product from sale or supply;
- (j) complaints about marketed products are examined, the causes of quality defects investigated, and appropriate measures taken in respect of the defective products to prevent recurrence.

### 3. Sanitation and hygiene

3.1 A high level of sanitation and hygiene should be practised in every aspect of the manufacture of drug products. The scope of sanitation and hygiene covers personnel, premises, equipment and apparatus, production materials and containers, products for cleaning and disinfection, and anything that could become a source of contamination to the product. Potential sources of contamination should be eliminated through an integrated comprehensive programme of sanitation and hygiene. (For *personal hygiene* see section 11, and for *sanitation* see section 12, "Premises".)

### 4. Qualification and validation

4.1 In accordance with GMP, each pharmaceutical company should identify what qualification and validation work is required to prove that the critical aspects of their particular operation are controlled.



4.2 The key elements of a qualification and validation programme of a company should be clearly defined and documented in a validation master plan.

4.3 Qualification and validation should establish and provide documentary evidence that:

- (a) the premises, supporting utilities, equipment and processes have been designed in accordance with the requirements for GMP (design qualification or DQ);
- (b) the premises, supporting utilities and equipment have been built and installed in compliance with their design specifications (installation qualification or IQ);
- (c) the premises, supporting utilities and equipment operate in accordance with their design specifications (operational qualification or OQ);
- (d) a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes (process validation or PV, also called performance qualification or PQ).

4.4 Any aspect of operation, including significant changes to the premises, facilities, equipment or processes, which may affect the quality of the product, directly or indirectly, should be qualified and validated.

4.5 Qualification and validation should not be considered as one-off exercises. An on-going programme should follow their first implementation and should be based on an annual review.

4.6 The commitment to maintain continued validation status should be stated in the relevant company documentation, such as the quality manual or validation master plan.

4.7 The responsibility of performing validation should be clearly defined.

4.8 Validation studies are an essential part of GMP and should be conducted in accordance with predefined and approved protocols.

4.9 A written report summarizing the results recorded and the conclusions reached should be prepared and stored.

4.10 Processes and procedures should be established on the basis of the results of the validation performed.

4.11 It is of critical importance that particular attention is paid to the validation of analytical test methods, automated systems and cleaning procedures.

## 5. Complaints

5.1 *Principle.* All complaints and other information concerning potentially defective products should be carefully reviewed according to written procedures and the corrective action should be taken.



## QUALITY ASSURANCE OF PHARMACEUTICALS

5.2 A person responsible for handling the complaints and deciding the measures to be taken should be designated, together with sufficient supporting staff to assist him or her. If this person is different from the authorized person, the latter should be made aware of any complaint, investigation or recall.

5.3 There should be written procedures describing the action to be taken, including the need to consider a recall, in the case of a complaint concerning a possible product defect.

5.4 Special attention should be given to establishing whether a complaint was caused because of counterfeiting.

5.5 Any complaint concerning a product defect should be recorded with all the original details and thoroughly investigated. The person responsible for quality control should normally be involved in the review of such investigations.

5.6 If a product defect is discovered or suspected in a batch, consideration should be given to whether other batches should be checked in order to determine whether they are also affected. In particular, other batches that may contain reprocessed product from the defective batch should be investigated.

5.7 Where necessary, appropriate follow-up action, possibly including product recall, should be taken after investigation and evaluation of the complaint.

5.8 All decisions made and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records.

5.9 Complaints records should be regularly reviewed for any indication of specific or recurring problems that require attention and might justify the recall of marketed products.

5.10 The competent authorities should be informed if a manufacturer is considering action following possibly faulty manufacture, product deterioration, counterfeiting or any other serious quality problems with a product.

## 6. Product recalls

6.1 *Principle.* There should be a system to recall from the market, promptly and effectively, products known or suspected to be defective.

6.2 The authorized person should be responsible for the execution and coordination of recalls. He/she should have sufficient staff to handle all aspects of the recalls with the appropriate degree of urgency.

6.3 There should be established written procedures, which are regularly reviewed and updated, for the organization of any recall activity. Recall operations should be capable of being initiated promptly down to the required level in the distribution chain.



## MAIN PRINCIPLES FOR PHARMACEUTICAL PRODUCTS

6.4 An instruction should be included in the written procedures to store recalled products in a secure segregated area while their fate is decided.

6.5 All competent authorities of all countries to which a given product has been distributed should be promptly informed of any intention to recall the product because it is, or is suspected of being, defective.

6.6 The distribution records should be readily available to the authorized person, and they should contain sufficient information on wholesalers and directly supplied customers (including, for exported products, those who have received samples for clinical tests and medical samples) to permit an effective recall.

6.7 The progress of the recall process should be monitored and recorded. Records should include the disposition of the product. A final report should be issued, including a reconciliation between the delivered and recovered quantities of the products.

6.8 The effectiveness of the arrangements for recalls should be tested and evaluated from time to time.

## 7. Contract production and analysis

7.1 *Principle.* Contract production and analysis must be correctly defined, agreed and controlled in order to avoid misunderstandings that could result in a product or work or analysis of unsatisfactory quality.

### General

7.2 All arrangements for contract manufacture and analysis, including any proposed changes in technical or other arrangements, should be in accordance with the marketing authorization for the product concerned.

7.3 The contract should permit the contract giver to audit the facilities of the contract acceptor.

7.4 In the case of contract analysis, the final approval for release must be given by the authorized person.

### The contract giver

7.5 The contract giver is responsible for assessing the competence of the contract acceptor in successfully carrying out the work or tests required, for approval for contract activities, and for ensuring by means of the contract that the principles of GMP described in this guide are followed.

7.6 The contract giver should provide the contract acceptor with all the information necessary to carry out the contracted operations correctly in accordance with



## QUALITY ASSURANCE OF PHARMACEUTICALS

the marketing authorization and any other legal requirements. The contract giver should ensure that the contract acceptor is fully aware of any problems associated with the product, work or tests that might pose a hazard to premises, equipment, personnel, other materials or other products.

7.7 The contract giver should ensure that all processed products and materials delivered by the contract acceptor comply with their specifications or that the product has been released by the authorized person.

### The contract acceptor

7.8 The contract acceptor must have adequate premises, equipment, knowledge, and experience and competent personnel to carry out satisfactorily the work ordered by the contract giver. Contract manufacture may be undertaken only by a manufacturer who holds a manufacturing authorization.

7.9 The contract acceptor should not pass to a third party any of the work entrusted to him or her under the contract without the contract giver's prior evaluation and approval of the arrangements. Arrangements made between the contract acceptor and any third party should ensure that the manufacturing and analytical information is made available in the same way as between the original contract giver and contract acceptor.

7.10 The contract acceptor should refrain from any activity that may adversely affect the quality of the product manufactured and/or analysed for the contract giver.

### The contract

7.11 There must be a written contract between the contract giver and the contract acceptor which clearly establishes the responsibilities of each party.

7.12 The contract must clearly state the way in which the authorized person, in releasing each batch of product for sale or issuing the certificate of analysis, exercises his or her full responsibility and ensures that each batch has been manufactured in, and checked for, compliance with the requirements of the marketing authorization.

7.13 Technical aspects of the contract should be drawn up by competent persons suitably knowledgeable in pharmaceutical technology, analysis and GMP.

7.14 All arrangements for production and analysis must be in accordance with the marketing authorization and agreed by both parties.

7.15 The contract should describe clearly who is responsible for purchasing, testing and releasing materials and for undertaking production and quality controls, including in-process controls, and who has responsibility for sampling and





analysis. In the case of contract analysis, the contract should state whether or not the contract acceptor should take samples at the premises of the manufacturer.

7.16 Manufacturing, analytical, distribution records and reference samples should be kept by, or be available to, the contract giver. Any records relevant to assessing the quality of a product in the event of complaints or a suspected defect must be accessible and specified in the defect/recall procedures of the contract giver.

7.17 The contract should describe the handling of starting materials, intermediate and bulk products and finished products if they are rejected. It should also describe the procedure to be followed if the contract analysis shows that the tested product must be rejected.

## 8. Self-inspection and quality audits

8.1 *Principle.* The purpose of self-inspection is to evaluate the manufacturer's compliance with GMP in all aspects of production and quality control. The self-inspection programme should be designed to detect any shortcomings in the implementation of GMP and to recommend the necessary corrective actions. Self-inspections should be performed routinely, and may be, in addition, performed on special occasions, e.g. in the case of product recalls or repeated rejections, or when an inspection by the health authorities is announced. The team responsible for self-inspection should consist of personnel who can evaluate the implementation of GMP objectively. All recommendations for corrective action should be implemented. The procedure for self-inspection should be documented, and there should be an effective follow-up programme.

### Items for self-inspection

8.2 Written instructions for self-inspection should be established to provide a minimum and uniform standard of requirements. These may include questionnaires on GMP requirements covering at least the following items:

- (a) personnel;
- (b) premises including personnel facilities;
- (c) maintenance of buildings and equipment;
- (d) storage of starting materials and finished products;
- (e) equipment;
- (f) production and in-process controls;
- (g) quality control;
- (h) documentation;
- (i) sanitation and hygiene;
- (j) validation and revalidation programmes;
- (k) calibration of instruments or measurement systems;



## QUALITY ASSURANCE OF PHARMACEUTICALS

- (l) recall procedures;
- (m) complaints management;
- (n) labels control;
- (o) results of previous self-inspections and any corrective steps taken.

### Self-inspection team

8.3 Management should appoint a self-inspection team consisting of experts in their respective fields and familiar with GMP. The members of the team may be appointed from inside or outside the company.

### Frequency of self-inspection

8.4 The frequency at which self-inspections are conducted may depend on company requirements but should preferably be at least once a year. The frequency should be stated in the procedure.

### Self-inspection report

8.5 A report should be made at the completion of a self-inspection. The report should include:

- (a) self-inspection results;
- (b) evaluation and conclusions;
- (c) recommended corrective actions.

### Follow-up action

8.6 There should be an effective follow-up programme. The company management should evaluate both the self-inspection report and the corrective actions as necessary.

### Quality audit

8.7 It may be useful to supplement self-inspections with a quality audit. A quality audit consists of an examination and assessment of all or part of a quality system with the specific purpose of improving it. A quality audit is usually conducted by outside or independent specialists or a team designated by the management for this purpose. Such audits may also be extended to suppliers and contractors (see section 7, "Contract production and analysis").



## Suppliers' audits and approval

8.8 The person responsible for quality control should have responsibility together with other relevant departments for approving suppliers who can reliably supply starting and packaging materials that meet established specifications.

8.9 Before suppliers are approved and included in the approved supplier's list or specifications, they should be evaluated. The evaluation should take into account a supplier's history and the nature of the materials to be supplied. If an audit is required, it should determine the supplier's ability to conform with GMP standards.

## 9. Personnel

9.1 *Principle.* The establishment and maintenance of a satisfactory system of quality assurance and the correct manufacture and control of pharmaceutical products and active ingredients rely upon people. For this reason there must be sufficient qualified personnel to carry out all the tasks for which the manufacturer is responsible. Individual responsibilities should be clearly defined and understood by the persons concerned and recorded as written descriptions.

### General

9.2 The manufacturer should have an adequate number of personnel with the necessary qualifications and practical experience. The responsibilities placed on any one individual should not be so extensive so as to present any risk to quality.

9.3. All responsible staff should have their specific duties recorded in written descriptions and adequate authority to carry out their responsibilities. Their duties may be delegated to designated deputies of a satisfactory qualification level. There should be no gaps or unexplained overlaps in the responsibilities of personnel concerned with the application of GMP. The manufacturer should have an organization chart.

9.4 All personnel should be aware of the principles of GMP that affect them and receive initial and continuing training, including hygiene instructions, relevant to their needs. All personnel should be motivated to support the establishment and maintenance of high-quality standards.

9.5 Steps should be taken to prevent unauthorized people from entering production, storage and quality control areas. Personnel who do not work in these areas should not use them as a passageway.



## QUALITY ASSURANCE OF PHARMACEUTICALS

### Key personnel

9.6 Key personnel include the head of production, the head of quality control and the authorized person. Normally, key posts should be occupied by full-time personnel. The heads of production and quality control should be independent of each other. In large organizations, it may be necessary to delegate some of the functions; however, the responsibility cannot be delegated.

9.7 Key personnel responsible for supervising the manufacture and quality control of pharmaceutical products should possess the qualifications of a scientific education and practical experience required by national legislation. Their education should include the study of an appropriate combination of:

- (a) chemistry (analytical or organic) or biochemistry;
- (b) chemical engineering;
- (c) microbiology;
- (d) pharmaceutical sciences and technology;
- (e) pharmacology and toxicology;
- (f) physiology;
- (g) other related sciences.

They should also have adequate practical experience in the manufacture and quality assurance of pharmaceutical products. In order to gain such experience, a preparatory period may be required, during which they should exercise their duties under professional guidance. The scientific education and practical experience of experts should be such as to enable them to exercise independent professional judgement, based on the application of scientific principles and understanding to the practical problems encountered in the manufacture and quality control of pharmaceutical products.

9.8 The heads of the production and quality control generally have some shared, or jointly exercised, responsibilities relating to quality. These may include, depending on national regulations:

- (a) authorization of written procedures and other documents, including amendments;
- (b) monitoring and control of the manufacturing environment;
- (c) plant hygiene;
- (d) process validation and calibration of analytical apparatus;
- (e) training, including the application and principles of quality assurance;
- (f) approval and monitoring of suppliers of materials;
- (g) approval and monitoring of contract manufacturers;
- (h) designation and monitoring of storage conditions for materials and products;
- (i) performance and evaluation of in-process controls;
- (j) retention of records;
- (k) monitoring of compliance with GMP requirements;



## MAIN PRINCIPLES FOR PHARMACEUTICAL PRODUCTS

- (l) inspection, investigation and taking of samples in order to monitor factors that may affect product quality.

9.9 The head of the production generally has the following responsibilities:

- (a) to ensure that products are produced and stored according to the appropriate documentation in order to obtain the required quality;
- (b) to approve the instructions relating to production operations, including the in-process controls, and to ensure their strict implementation;
- (c) to ensure that the production records are evaluated and signed by a designated person;
- (d) to check the maintenance of the department, premises, and equipment;
- (e) to ensure that the appropriate process validations and calibrations of control equipment are performed and recorded and the reports made available;
- (f) to ensure that the required initial and continuing training of production personnel is carried out and adapted according to need.

9.10 The head of the quality control generally has the following responsibilities:

- (a) to approve or reject starting materials, packaging materials, and intermediate, bulk and finished products in relation with their specifications;
- (b) to evaluate batch records;
- (c) to ensure that all necessary testing is carried out;
- (d) to approve sampling instructions, specifications, test methods and other quality control procedures;
- (e) to approve and monitor analyses carried out under contract;
- (f) to check the maintenance of the department, premises and equipment;
- (g) to ensure that the appropriate validations, including those of analytical procedures, and calibrations of control equipment are carried out;
- (h) to ensure that the required initial and continuing training of quality control personnel is carried out and adapted according to need.

Other duties of the quality control are summarized in sections 17.3 and 17.4.

9.11 The authorized person is responsible for compliance with technical or regulatory requirements related to the quality of finished products and the approval of the release of the finished product for sale.

9.12 The authorized person will also be involved in other activities, including the following:

- (a) implementation (and, when needed, establishment) of the quality system;
- (b) participation in the development of the company's quality manual;
- (c) supervision of the regular internal audits or self-inspections;
- (d) oversight of the quality control department;
- (e) participation in external audit (vendor audit);
- (f) participation in validation programmes.



## QUALITY ASSURANCE OF PHARMACEUTICALS

9.13 The function of the approval of the release of a finished batch or a product can be delegated to a designated person with appropriate qualifications and experience who will release the product in accordance with an approved procedure. This is normally done by quality assurance by means of batch review.

9.14 The person responsible for approving a batch for release should always ensure that the following requirements have been met:

- (a) the marketing authorization and the manufacturing authorization requirements for the product have been met for the batch concerned;
- (b) the principles and guidelines of GMP, as laid down in the guidelines published by WHO, have been followed;
- (c) the principal manufacturing and testing processes have been validated, if different;
- (d) all the necessary checks and tests have been performed and account taken of the production conditions and manufacturing records;
- (e) any planned changes or deviations in manufacturing or quality control have been notified in accordance with a well defined reporting system before any product is released. Such changes may need notification to, and approval by, the drug regulatory authority;
- (f) any additional sampling, inspection, tests and checks have been carried out or initiated, as appropriate, to cover planned changes and deviations;
- (g) all necessary production and quality control documentation has been completed and endorsed by supervisors trained in appropriate disciplines;
- (h) appropriate audits, self-inspections and spot-checks are carried out by experienced and trained staff;
- (i) approval has been given by the head of quality control;
- (j) all relevant factors have been considered, including any not specifically associated with the output batch directly under review (e.g. subdivision of output batches from a common input, factors associated with continuous production runs).

## 10. Training

10.1 The manufacturer should provide training in accordance with a written programme for all personnel whose duties take them into manufacturing areas or into control laboratories (including the technical, maintenance and cleaning personnel) and for other personnel as required.

10.2 Besides basic training on the theory and practice of GMP, newly recruited personnel should receive training appropriate to the duties assigned to them. Continuing training should also be given, and its practical effectiveness periodically assessed. Approved training programmes should be available. Training records should be kept.



## MAIN PRINCIPLES FOR PHARMACEUTICAL PRODUCTS

10.3 Personnel working in areas where contamination is a hazard, e.g. clean areas or areas where highly active, toxic, infectious or sensitizing materials are handled, should be given specific training.

10.4 The concept of quality assurance and all the measures which aid its understanding and implementation should be fully discussed during the training sessions.

10.5 Visitors or untrained personnel should preferably not be taken into the production and quality control areas. If this is unavoidable, they should be given relevant information in advance (particularly about personal hygiene) and the prescribed protective clothing. They should be closely supervised.

10.6 Consultant and contract staff should be qualified for the services they provide. Evidence of this should be included in the training records.

### 11. Personal hygiene

11.1 All personnel, prior to and during employment, as appropriate, should undergo health examinations. Personnel conducting visual inspections should also undergo periodic eye examinations.

11.2 All personnel should be trained in the practices of personal hygiene. A high level of personal hygiene should be observed by all those concerned with manufacturing processes. In particular, personnel should be instructed to wash their hands before entering production areas. Signs to this effect should be posted and instructions observed.

11.3 Any person shown at any time to have an apparent illness or open lesions that may adversely affect the quality of products should not be allowed to handle starting materials, packaging materials, in-process materials or drug products until the condition is no longer judged to be a risk.

11.4 All employees should be instructed and encouraged to report to their immediate supervisor any conditions (relating to plant, equipment or personnel) that they consider may adversely affect the products.

11.5 Direct contact should be avoided between the operator's hands and starting materials, primary packaging materials and intermediate or bulk product.

11.6 To ensure protection of the product from contamination, personnel should wear clean body coverings appropriate to the duties they perform, including appropriate hair covering. Used clothes, if reusable, should be stored in separate closed containers until properly laundered and, if necessary, disinfected or sterilized.

11.7 Smoking, eating, drinking, chewing, and keeping plants, food, drink, smoking material and personal medicines should not be permitted in production,



laboratory and storage areas, or in any other areas where they might adversely influence product quality.

11.8 Personal hygiene procedures including the use of protective clothing should apply to all persons entering production areas, whether they are temporary or full-time employees or non-employees, e.g. contractors' employees, visitors, senior managers, and inspectors.

## 12. Premises

12.1 *Principle*. Premises must be located, designed, constructed, adapted, and maintained to suit the operations to be carried out.

### General

12.2 The layout and design of premises must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products.

12.3 Where dust is generated (e.g. during sampling, weighing, mixing and processing operations, packaging of powder), measures should be taken to avoid cross-contamination and facilitate cleaning.

12.4 Premises should be situated in an environment that, when considered together with measures to protect the manufacturing process, presents minimum risk of causing any contamination of materials or products.

12.5 Premises used for the manufacture of finished products should be suitably designed and constructed to facilitate good sanitation.

12.6 Premises should be carefully maintained, and it should be ensured that repair and maintenance operations do not present any hazard to the quality of products.

12.7 Premises should be cleaned and, where applicable, disinfected according to detailed written procedures. Records should be maintained.

12.8 Electrical supply, lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the pharmaceutical products during their manufacture and storage, or the accurate functioning of equipment.

12.9 Premises should be designed and equipped so as to afford maximum protection against the entry of insects, birds or other animals. There should be a procedure for rodent and pest control.





## MAIN PRINCIPLES FOR PHARMACEUTICAL PRODUCTS

12.10 Premises should be designed to ensure the logical flow of materials and personnel.

### Ancillary areas

12.11 Rest and refreshment rooms should be separate from manufacturing and control areas.

12.12 Facilities for changing and storing clothes and for washing and toilet purposes should be easily accessible and appropriate for the number of users. Toilets should not communicate directly with production or storage areas.

12.13 Maintenance workshops should if possible be separated from production areas. Whenever parts and tools are stored in the production area, they should be kept in rooms or lockers reserved for that use.

12.14 Animal houses should be well isolated from other areas, with separate entrance (animal access) and air-handling facilities.

### Storage areas

12.15 Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products with proper separation and segregation: starting and packaging materials, intermediates, bulk and finished products, products in quarantine, and released, rejected, returned or recalled products.

12.16 Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean, dry, sufficiently lit and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity) these should be provided, controlled, monitored and recorded where appropriate.

12.17 Receiving and dispatch bays should be separated and protect materials and products from the weather. Receiving areas should be designed and equipped to allow containers of incoming materials to be cleaned if necessary before storage.

12.18 Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access restricted to authorized personnel. Any system replacing the physical quarantine should give equivalent security.

12.19 Segregation should be provided for the storage of rejected, recalled, or returned materials or products.

12.20 Highly active and radioactive materials, narcotics, other dangerous drugs, and substances presenting special risks of abuse, fire or explosion should be stored in safe and secure areas.



## QUALITY ASSURANCE OF PHARMACEUTICALS

12.21 Printed packaging materials are considered critical to the conformity of the pharmaceutical product to its labelling and special attention should be paid to sampling and the safe and secure storage of these materials.

12.22 There should normally be a separate sampling area for starting materials. (If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination.)

### Weighing areas

12.23 The weighing of starting materials and the estimation of yield by weighing should be carried out in separate weighing areas designed for that use, for example with provisions for dust control. Such areas may be part of either storage or production areas.

### Production areas

12.24 In order to minimize the risk of a serious medical hazard due to cross-contamination, dedicated and self-contained facilities must be available for the production of particular pharmaceutical products, such as highly sensitizing materials (e.g. penicillins) or biological preparations (e.g. live microorganisms). The production of certain other highly active products, such as some antibiotics, hormones, cytotoxic substances and certain non-pharmaceutical products, should not be conducted in the same facilities. In exceptional cases, the principle of campaign working in the same facilities can be accepted provided that specific precautions are taken and the necessary validations (including cleaning validation) are made. The manufacture of technical poisons, such as pesticides and herbicides, should not be allowed in premises used for the manufacture of pharmaceutical products.

12.25 Premises should preferably be laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.

12.26 The adequacy of the working and in-process storage space should permit the orderly and logical positioning of equipment and materials so as to minimize the risk of confusion between different pharmaceutical products or their components, to avoid cross-contamination, and to minimize the risk of omission or wrong application of any of the manufacturing or control steps.

12.27 Where starting and primary packaging materials and intermediate or bulk products are exposed to the environment, interior surfaces (walls, floors and ceilings) should be smooth and free from cracks and open joints, should not shed particulate matter, and should permit easy and effective cleaning and, if necessary, disinfection.



## MAIN PRINCIPLES FOR PHARMACEUTICAL PRODUCTS

12.28 Pipework, light fittings, ventilation points and other services should be designed and sited to avoid the creation of recesses that are difficult to clean. As far as possible, for maintenance purposes, they should be accessible from outside the manufacturing areas.

12.29 Drains should be of adequate size and designed and equipped to prevent back-flow. Open channels should be avoided where possible, but if they are necessary they should be shallow to facilitate cleaning and disinfection.

12.30 Production areas should be effectively ventilated, with air-control facilities (including filtration of air to a sufficient level to prevent contamination and cross-contamination, as well as control of temperature and, where necessary, humidity) appropriate to the products handled, to the operations undertaken and to the external environment. These areas should be regularly monitored during both production and non-production periods to ensure compliance with their design specifications.

12.31 Premises for the packaging of pharmaceutical products should be specifically designed and laid out so as to avoid mix-ups or cross-contamination.

12.32 Production areas should be well lit, particularly where visual on-line controls are carried out.

### Quality control areas

12.33 Quality control laboratories should be separated from production areas. Areas where biological, microbiological or radioisotope test methods are employed should be separated from each other.

12.34 Quality control laboratories should be designed to suit the operations to be carried out in them. Sufficient space should be given to avoid mix-ups and cross-contamination. There should be adequate suitable storage space for samples, reference standards (if necessary, with cooling), solvents, reagents and records.

12.35 The design of the laboratories should take into account the suitability of construction materials, prevention of fumes and ventilation. There should be separate air supply to laboratories and production areas. Separate air-handling units and other provisions are needed for biological, microbiological and radioisotope laboratories.

12.36 A separate room may be needed for instruments to protect them against electrical interference, vibration, contact with excessive moisture and other external factors, or where it is necessary to isolate the instruments.



### 13. Equipment

13.1 Equipment must be located, designed, constructed, adapted, and maintained to suit the operations to be carried out. The layout and design of equipment must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products.

13.2 Equipment should be installed in such a way as to minimize any risk of error or of contamination.

13.3 Fixed pipework should be clearly labelled to indicate the contents and, where applicable, the direction of flow.

13.4 All service pipings and devices should be adequately marked and special attention paid to the provision of non-interchangeable connections or adaptors for dangerous gases and liquids.

13.5 Balances and other measuring equipment of an appropriate range and precision should be available for production and control operations and should be calibrated on a scheduled basis.

13.6 Production equipment should be thoroughly cleaned on a scheduled basis.

13.7 Laboratory equipment and instruments should be suited to the testing procedures undertaken.

13.8 Washing, cleaning and drying equipment should be chosen and used so as not to be a source of contamination.

13.9 Production equipment should not present any hazard to the products. The parts of the production equipment that come into contact with the product must not be reactive, additive, or absorptive to an extent that would affect the quality of the product.

13.10 Defective equipment should be removed from production and quality control areas. If this is not possible, it should be clearly labelled as defective to prevent use.

13.11 Closed equipment should be used whenever appropriate. Where open equipment is used or equipment is opened, precautions should be taken to minimize contamination.

13.12 Non-dedicated equipment should be cleaned according to validated cleaning procedures between production of different pharmaceutical products to prevent cross-contamination.

13.13 Current drawings of critical equipment and support systems should be maintained.



## 14. Materials

14.1 *Principle.* The main objective of a pharmaceutical plant is to produce finished products for patients' use from a combination of materials (starting and packaging).

14.2 Materials include starting materials, packaging materials, gases, solvents, process aids, reagents and labelling materials.

### General

14.3 No materials used for operations such as cleaning, lubrication of equipment and pest control, should come into direct contact with the product. Where possible, such materials should be of a suitable grade (e.g. food grade) to minimize health risks.

14.4 All incoming materials and finished products should be quarantined immediately after receipt or processing, until they are released for use or distribution.

14.5 All materials and products should be stored under the appropriate conditions established by the manufacturer and in an orderly fashion to permit batch segregation and stock rotation by a first-expire, first-out rule.

14.6. Water used in the manufacture of pharmaceutical products should be suitable for its intended use.

### Starting materials

14.7 The purchase of starting materials is an important operation that should involve staff who have a particular and thorough knowledge of the products and suppliers.

14.8 Starting materials should be purchased only from approved suppliers and, where possible, directly from the producer. It is also recommended that the specifications established by the manufacturer for the starting materials be discussed with the suppliers. It is of benefit that all critical aspects of the production and control of the starting material in question, including handling, labelling and packaging requirements as well as complaints and rejection procedures, are contractually agreed between the manufacturer and the supplier.

14.9 For each consignment, the containers should be checked for at least integrity of package and seal and for correspondence between the order, the delivery note, and the supplier's labels.

14.10 All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and



## QUALITY ASSURANCE OF PHARMACEUTICALS

labelled, if required, with the prescribed information. Where additional labels are attached to containers, the original information should not be lost.

14.11 Damage to containers and any other problem that might adversely affect the quality of a material should be recorded and reported to the quality control department and investigated.

14.12 If one delivery of material is made up of different batches, each batch must be considered as separate for sampling, testing and release.

14.13 Starting materials in the storage area should be appropriately labelled. Labels should bear at least the following information:

- (a) the designated name of the product and the internal code reference where applicable;
- (b) the batch number given by the supplier and, on receipt, the control or batch number given by the manufacturer, if any, documented so as to ensure traceability;
- (c) the status of the contents (e.g. on quarantine, on test, released, rejected, returned, recalled);
- (d) where appropriate, an expiry date or a date beyond which retesting is necessary.

When fully validated computerized storage systems are used, not all of the above information need be in a legible form on the label.

14.14 There should be appropriate procedures or measures to ensure the identity of the contents of each container of starting material. Bulk containers from which samples have been drawn should be identified.

14.15 Only starting materials released by the quality control department and within their shelf-life should be used.

14.16 Starting materials should be dispensed only by designated persons, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers.

14.17 Each dispensed material and its weight or volume should be independently checked and the check recorded.

14.18 Materials dispensed for each batch of the final product should be kept together and conspicuously labelled as such.

### Packaging materials

14.19 The purchase, handling and control of primary and printed packaging materials should be as for starting materials.



## MAIN PRINCIPLES FOR PHARMACEUTICAL PRODUCTS

14.20 Particular attention should be paid to printed packaging materials. They should be stored in secure conditions so as to exclude the possibility of unauthorized access. Roll feed labels should be used wherever possible. Cut labels and other loose printed materials should be stored and transported in separate closed containers so as to avoid mix-ups. Packaging materials should be issued for use only by designated personnel following an approved and documented procedure.

14.21 Each delivery or batch of printed or primary packaging material should be given a specific reference number or identification mark.

14.22 Outdated or obsolete primary packaging material or printed packaging material should be destroyed and its disposal recorded.

14.23 All products and packaging materials to be used should be checked on delivery to the packaging department for quantity, identity and conformity with the packaging instructions.

### Intermediate and bulk products

14.24 Intermediate and bulk products should be kept under appropriate conditions.

14.25 Intermediate and bulk products purchased as such should be handled on receipt as though they were starting materials.

### Finished products

14.26 Finished products should be held in quarantine until their final release, after which they should be stored as usable stock under conditions established by the manufacturer.

14.27 The evaluation of finished products and the documentation necessary for release of a product for sale are described in section 17, "Good practices in quality control".

### Rejected, recovered, reprocessed and reworked materials

14.28 Rejected materials and products should be clearly marked as such and stored separately in restricted areas. They should either be returned to the suppliers or, where appropriate, reprocessed or destroyed in a timely manner. Whatever action is taken should be approved by authorized personnel and recorded.

14.29 The reworking or recovery of rejected products should be exceptional. It is permitted only if the quality of the final product is not affected, if the specifications are met, and if it is done in accordance with a defined and authorized procedure after evaluation of the risks involved. A record should be kept



## QUALITY ASSURANCE OF PHARMACEUTICALS

of the reworking or recovery. A reworked batch should be given a new batch number.

14.30 The introduction of all or part of earlier batches, conforming to the required quality, into a batch of the same product at a defined stage of manufacture should be authorized beforehand. This recovery should be carried out in accordance with a defined procedure after evaluation of the risks involved, including any possible effect on shelf-life. The recovery should be recorded.

14.31 The need for additional testing of any finished product that has been reprocessed, reworked or into which a recovered product has been incorporated, should be considered by the quality control department.

### Recalled products

14.32 Recalled products should be identified and stored separately in a secure area until a decision is taken on their fate. The decision should be made as soon as possible.

### Returned goods

14.33 Products returned from the market should be destroyed unless it is certain that their quality is satisfactory; in such cases they may be considered for resale or relabelling, or alternative action taken only after they have been critically assessed by the quality control function in accordance with a written procedure. The nature of the product, any special storage conditions it requires, its condition and history, and the time elapsed since it was issued should all be taken into account in this assessment. Where any doubt arises over the quality of the product, it should not be considered suitable for reissue or reuse. Any action taken should be appropriately recorded.

### Reagents and culture media

14.34 There should be records for the receipt and preparation of reagents and culture media.

14.35 Reagents made up in the laboratory should be prepared according to written procedures and appropriately labelled. The label should indicate the concentration, standardization factor, shelf-life, the date when restandardization is due, and the storage conditions. The label should be signed and dated by the person preparing the reagent.

14.36 Both positive and negative controls should be applied to verify the suitability of culture media each time they are prepared and used. The size of the inoculum used in positive controls should be appropriate to the sensitivity required.





## MAIN PRINCIPLES FOR PHARMACEUTICAL PRODUCTS

### Reference standards

14.37 Whenever official reference standards exist, these should preferably be used.

14.38 Official reference standards should be used only for the purpose described in the appropriate monograph.

14.39 Reference standards prepared by the producer should be tested, released and stored in the same way as official standards. They should be kept under the responsibility of a designated person in a secure area.

14.40 Secondary or working standards may be established by the application of appropriate tests and checks at regular intervals to ensure standardization.

14.41 Reference standards should be properly labelled with at least the following information:

- (a) name of the material;
- (b) batch or lot number and control number;
- (c) date of preparation;
- (d) shelf-life;
- (e) potency;
- (f) storage conditions.

14.42 All in-house reference standards should be standardized against an official reference standard, when available, initially and at regular intervals thereafter.

14.43 All reference standards should be stored and used in a manner that will not adversely affect their quality.

### Waste materials

14.44 Provision should be made for the proper and safe storage of waste materials awaiting disposal. Toxic substances and flammable materials should be stored in suitably designed, separate, enclosed cupboards, as required by national legislation.

14.45 Waste material should not be allowed to accumulate. It should be collected in suitable receptacles for removal to collection points outside the buildings and disposed of safely and in a sanitary manner at regular and frequent intervals.

### Miscellaneous

14.46 Rodenticides, insecticides, fumigating agents and sanitizing materials should not be permitted to contaminate equipment, starting materials, packaging materials, in-process materials or finished products.



## 15. Documentation

15.1 *Principle.* Good documentation is an essential part of the quality assurance system and, as such, should exist for all aspects of GMP. Its aims are to define the specifications and procedures for all materials and methods of manufacture and control; to ensure that all personnel concerned with manufacture know what to do and when to do it; to ensure that authorized persons have all the information necessary to decide whether or not to release a batch of a drug for sale, to ensure the existence of documented evidence, traceability, and to provide records and an audit trail that will permit investigation. It ensures the availability of the data needed for validation, review and statistical analysis. The design and use of documents depend upon the manufacturer. In some cases some or all of the documents described below may be brought together, but they will usually be separate.

### General

15.2 Documents should be designed, prepared, reviewed and distributed with care. They should comply with the relevant parts of the manufacturing and marketing authorizations.

15.3 Documents should be approved, signed and dated by the appropriate responsible persons. No document should be changed without authorization and approval.

15.4 Documents should have unambiguous contents: the title, nature and purpose should be clearly stated. They should be laid out in an orderly fashion and be easy to check. Reproduced documents should be clear and legible. The reproduction of working documents from master documents must not allow any error to be introduced through the reproduction process.

15.5 Documents should be regularly reviewed and kept up to date. When a document has been revised, a system should exist to prevent inadvertent use of the superseded version. Superseded documents should be retained for a specific period of time.

15.6 Where documents require the entry of data, these entries should be clear, legible and indelible. Sufficient space should be provided for such entries.

15.7 Any alteration made to a document should be signed and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.

15.8 Records should be made or completed when any action is taken and in such a way that all significant activities concerning the manufacture of pharmaceutical products are traceable. Records should be retained for at least one year after the expiry date of the finished product.



15.9 Data (and records for storage) may be recorded by electronic data-processing systems or by photographic or other reliable means. Master formulae and detailed standard operating procedures relating to the system in use should be available and the accuracy of the records should be checked. If documentation is handled by electronic data-processing methods, only authorized persons should be able to enter or modify data in the computer, and there should be a record of changes and deletions; access should be restricted by passwords or other means and the entry of critical data should be independently checked. Batch records stored electronically should be protected by back-up transfer on magnetic tape, microfilm, paper print-outs or other means. It is particularly important that, during the period of retention, the data are readily available.

## Documents required

### **Labels**

15.10 Labels applied to containers, equipment or premises should be clear, unambiguous and in the company's agreed format. It is often helpful in addition to the wording on the labels to use colours to indicate status (e.g. quarantined, accepted, rejected, clean).

15.11 All finished drug products should be identified by labelling, as required by the national legislation, bearing at least the following information:

- (a) the name of the drug product;
- (b) a list of the active ingredients (if applicable, with the INNs), showing the amount of each present and a statement of the net contents (e.g. number of dosage units, weight, volume);
- (c) the batch number assigned by the manufacturer;
- (d) the expiry date in an uncoded form;
- (e) any special storage conditions or handling precautions that may be necessary;
- (f) directions for use, and warnings and precautions that may be necessary;
- (g) the name and address of the manufacturer or the company or the person responsible for placing the product on the market.

15.12 For reference standards, the label and/or accompanying document should indicate potency or concentration, date of manufacture, expiry date, date the closure is first opened, storage conditions and control number, as appropriate.

### **Specifications and testing procedures**

15.13 Testing procedures described in documents should be validated in the context of available facilities and equipment before they are adopted for routine testing.



## QUALITY ASSURANCE OF PHARMACEUTICALS

15.14 There should be appropriately authorized and dated specifications, including tests on identity, content, purity and quality, for starting and packaging materials and for finished products; where appropriate, they should also be available for intermediate or bulk products. Specifications for water, solvents and reagents (e.g. acids and bases) used in production should be included.

15.15 Each specification should be approved, signed and dated, and maintained by quality control, quality assurance unit or documentation centre. Specifications for starting materials, intermediates, and bulk, finished products and packaging materials are referred to in sections 15.18–15.21.

15.16 Periodic revisions of the specifications may be necessary to comply with new editions of the national pharmacopoeia or other official compendia.

15.17 Pharmacopoeias, reference standards, reference spectra and other reference materials should be available in the quality control laboratory.

### ***Specifications for starting and packaging materials***

15.18 Specifications for starting, primary and printed packaging materials should provide, if applicable, a description of the materials, including:

- (a) the designated name (if applicable, the INN) and internal code reference;
- (b) the reference, if any, to a pharmacopoeial monograph;
- (c) qualitative and quantitative requirements with acceptance limits.

Depending on the company's practice other data may be added to the specification, such as:

- (a) the supplier and the original producer of the materials;
- (b) a specimen of printed materials;
- (c) directions for sampling and testing, or a reference to procedures;
- (d) storage conditions and precautions;
- (e) the maximum period of storage before re-examination.

Packaging material should conform to specifications, and should be compatible with the material and/or with the drug product it contains. The material should be examined for compliance with the specification, and for defects as well as for the correctness of identity markings.

15.19 Documents describing testing procedures should state the required frequency for re-assaying each starting material, as determined by its stability.

### ***Specifications for intermediate and bulk products***

15.20 Specifications for intermediate and bulk products should be available. The specifications should be similar to specifications for starting materials or for finished products, as appropriate.



### ***Specifications for finished products***

15.21 Specifications for finished products should include:

- (a) the designated name of the product and the code reference, where applicable;
- (b) the designated name(s) of the active ingredient(s) (if applicable, with the INN(s));
- (c) the formula or a reference to the formula;
- (d) a description of the dosage form and package details;
- (e) directions for sampling and testing or a reference to procedures;
- (f) the qualitative and quantitative requirements, with acceptance limits;
- (g) the storage conditions and precautions, where applicable;
- (h) the shelf-life.

### ***Master formulae***

15.22 A formally authorized master formula should exist for each product and batch size to be manufactured.

15.23 The master formula should include:

- (a) the name of the product, with a product reference code relating to its specification;
- (b) a description of the dosage form, strength of the product and batch size;
- (c) a list of all starting materials to be used (if applicable, with the INNs), with the amount of each, described using the designated name and a reference that is unique to that material (mention should be made of any substance that may disappear in the course of processing);
- (d) a statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable;
- (e) a statement of the processing location and the principal equipment to be used;
- (f) the methods, or reference to the methods, to be used for preparing and operating the critical equipment, e.g. cleaning (especially after a change in product), assembling, calibrating, sterilizing, use;
- (g) detailed step-wise processing instructions (e.g. checks on materials, pre-treatments, sequence for adding materials, mixing times, temperatures);
- (h) the instructions for any in-process controls with their limits;
- (i) where necessary, the requirements for storage of the products, including the container, the labelling, and any special storage conditions;
- (j) any special precautions to be observed.



### ***Packaging instructions***

15.24 Formally authorized packaging instructions should exist for each product, pack size and type. These should normally include, or make reference to:

- (a) the name of the product;
- (b) a description of its pharmaceutical form, strength and, where applicable, method of application;
- (c) the pack size expressed in terms of the number, weight or volume of the product in the final container;
- (d) a complete list of all the packaging materials required for a standard batch size, including quantities, sizes and types, with the code or reference number relating to the specifications for each packaging material;
- (e) where appropriate, an example or reproduction of the relevant printed packaging materials and specimens, indicating where the batch number and expiry date of the product have been marked;
- (f) special precautions to be observed, including a careful examination of the packaging area and equipment in order to ascertain the line clearance before and after packaging operations;
- (g) a description of the packaging operation, including any significant subsidiary operations, and equipment to be used;
- (h) details of in-process controls with instructions for sampling and acceptance limits.

### ***Batch processing records***

15.25 A batch processing record should be kept for each batch processed. It should be based on the relevant parts of the currently approved specifications on the record. The method of preparation of such records should be designed to avoid errors. (Copying or validated computer programmes are recommended. Transcribing from approved documents should be avoided.)

15.26 Before any processing begins, a check should be made that the equipment and work station are clear of previous products, documents, or materials not required for the planned process, and that the equipment is clean and suitable for use. This check should be recorded.

15.27 During processing, the following information should be recorded at the time each action is taken, and after completion the record should be dated and signed by the person responsible for the processing operations:

- (a) the name of the product;
- (b) the number of the batch being manufactured;
- (c) dates and times of commencement, of significant intermediate stages, and of completion of production;
- (d) the name of the person responsible for each stage of production;



## MAIN PRINCIPLES FOR PHARMACEUTICAL PRODUCTS

- (e) the initials of the operator(s) of different significant steps of production and, where appropriate, of the person(s) who checked each of these operations (e.g. weighing);
- (f) the batch number and/or analytical control number and the quantity of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added);
- (g) any relevant processing operation or event and the major equipment used;
- (h) the in-process controls performed, the initials of the person(s) carrying them out, and the results obtained;
- (i) the amount of product obtained at different and pertinent stages of manufacture (yield), together with comments or explanations for significant deviations from the expected yield;
- (j) notes on special problems including details, with signed authorization for any deviation from the master formula.

### **Batch packaging records**

15.28 A batch packaging record should be kept for each batch or part batch processed. It should be based on the relevant parts of the approved packaging instructions, and the method of preparing such records should be designed to avoid errors. (Copying or validated computer programmes are recommended. Transcribing from approved documents should be avoided.)

15.29 Before any packaging operation begins, checks should be made that the equipment and work station are clear of previous products, documents or materials not required for the planned packaging operations, and that equipment is clean and suitable for use. These checks should be recorded.

15.30 The following information should be recorded at the time each action is taken, and the date and the person responsible should be clearly identified by signature or electronic password:

- (a) the name of the product, the batch number and the quantity of bulk product to be packed, as well as the batch number and the planned quantity of finished product that will be obtained, the quantity actually obtained and the reconciliation;
- (b) the date(s) and time(s) of the packaging operations;
- (c) the name of the responsible person carrying out the packaging operation;
- (d) the initials of the operators of the different significant steps;
- (e) the checks made for identity and conformity with the packaging instructions, including the results of in-process controls;
- (f) details of the packaging operations carried out, including references to equipment and the packaging lines used, and, when necessary, the instructions for keeping the product unpacked or a record of returning product that has not been packaged to the storage area;



## QUALITY ASSURANCE OF PHARMACEUTICALS

- (g) whenever possible, samples of the printed packaging materials used, including specimens bearing the approval for the printing of and regular check (where appropriate) of the batch number, expiry date, and any additional overprinting;
- (h) notes on any special problems, including details of any deviation from the packaging instructions, with written authorization by an appropriate person;
- (i) the quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of product obtained to permit an adequate reconciliation.

### ***Standard operating procedures (SOPs) and records***

15.31 Standard operating procedures and associated records of actions taken or, where appropriate, conclusions reached should be available for:

- (a) equipment assembly and validation;
- (b) analytical apparatus and calibration;
- (c) maintenance, cleaning and sanitization;
- (d) personnel matters including qualification, training, clothing and hygiene;
- (e) environmental monitoring;
- (f) pest control;
- (g) complaints;
- (h) recalls;
- (i) returns.

15.32 There should be standard operating procedures and records for the receipt of each delivery of starting material and primary and printed packaging material.

15.33 The records of the receipts should include:

- (a) the name of the material on the delivery note and the containers;
- (b) the “in-house” name and/or code of material if different from (a);
- (c) the date of receipt;
- (d) the supplier’s name and, if possible, manufacturer’s name;
- (e) the manufacturer’s batch or reference number;
- (f) the total quantity, and number of containers received;
- (g) the batch number assigned after receipt;
- (h) any relevant comment (e.g. state of the containers).

15.34 There should be standard operating procedures for the internal labelling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.

15.35 Standard operating procedures should be available for each instrument and piece of equipment (e.g. use, calibration, cleaning, maintenance) and placed in close proximity to the equipment.





## MAIN PRINCIPLES FOR PHARMACEUTICAL PRODUCTS

15.36 There should be standard operating procedures for sampling, which specify the person(s) authorized to take samples.

15.37 The sampling instructions should include:

- (a) the method of sampling and the sampling plan;
- (b) the equipment to be used;
- (c) any precautions to be observed to avoid contamination of the material or any deterioration in its quality;
- (d) the amount(s) of sample(s) to be taken;
- (e) instructions for any required subdivision of the sample;
- (f) the type of sample container(s) to be used, and whether they are for aseptic sampling or for normal sampling, and labelling;
- (g) any specific precautions to be observed, especially in regard to the sampling of sterile or noxious material.

15.38 There should be a standard operating procedure describing the details of the batch (lot) numbering system, with the objective of ensuring that each batch of intermediate, bulk or finished product is identified with a specific batch number.

15.39 The standard operating procedures for batch numbering that are applied to the processing stage and to the respective packaging stage should be related to each other.

15.40 The standard operating procedure for batch numbering should ensure that the same batch numbers will not be used repeatedly; this applies also to reprocessing.

15.41 Batch-number allocation should be immediately recorded, e.g. in a log-book. The record should include at least the date of allocation, product identity and size of batch.

15.42 There should be written procedures for testing materials and products at different stages of manufacture, describing the methods and equipment to be used. The tests performed should be recorded.

15.43 Analysis records should include at least the following data:

- (a) the name of the material or product and, where applicable, dosage form;
- (b) the batch number and, where appropriate, the manufacturer and/or supplier;
- (c) references to the relevant specifications and testing procedures;
- (d) test results, including observations and calculations, and reference to any specifications (limits);
- (e) date(s) and reference number(s) of testing;
- (f) the initials of the persons who performed the testing;
- (g) the date and initials of the persons who verified the testing and the calculations, where appropriate;



## QUALITY ASSURANCE OF PHARMACEUTICALS

(h) a clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person.

15.44 Written release and rejection procedures should be available for materials and products, and in particular for the release for sale of the finished product by an authorized person.

15.45 Records should be maintained of the distribution of each batch of a product in order, e.g. to facilitate the recall of the batch if necessary.

15.46 Records should be kept for major and critical equipment, as appropriate, of any validations, calibrations, maintenance, cleaning, or repair operations, including dates and the identity of the people who carried these operations out.

15.47 The use of major and critical equipment and the areas where products have been processed should be appropriately recorded in chronological order.

15.48 There should be written procedures assigning responsibility for cleaning and sanitation and describing in sufficient detail the cleaning schedules, methods, equipment and materials to be used and facilities and equipment to be cleaned. Such written procedures should be followed.

## 16. Good practices in production

16.1 *Principle.* Production operations must follow clearly defined procedures in accordance with manufacturing and marketing authorizations, with the objective of obtaining products of the requisite quality.

### General

16.2 All handling of materials and products, such as receipt and cleaning, quarantine, sampling, storage, labelling, dispensing, processing, packaging and distribution should be done in accordance with written procedures or instructions and, where necessary, recorded.

16.3 Any deviation from instructions or procedures should be avoided as far as possible. If deviations occur, they should be done in accordance with an approved procedure. The authorization of the deviation should be approved in writing by a designated person, with the involvement of the quality control department, when appropriate.

16.4 Checks on yields and reconciliation of quantities should be carried out as necessary to ensure that there are no discrepancies outside acceptable limits.

16.5 Operations on different products should not be carried out simultaneously or consecutively in the same room or area unless there is no risk of mix-up or cross-contamination.



## MAIN PRINCIPLES FOR PHARMACEUTICAL PRODUCTS

16.6 At all times during processing, all materials, bulk containers, major items of equipment, and where appropriate, the rooms and packaging lines being used should be labelled or otherwise identified with an indication of the product or material being processed, its strength (where applicable) and the batch number. Where applicable, this indication should also mention the stage of production. In some cases it may be useful to record also the name of the previous product that has been processed.

16.7 Access to production premises should be restricted to authorized personnel.

16.8 Normally, non-medicinal products should not be produced in areas or with equipment destined for the production of pharmaceutical products.

16.9 In-process controls are usually performed within the production area. The performance of such in-process controls should not have any negative effect on the quality of the product or another product (e.g. cross-contamination or mix-up).

### Prevention of cross-contamination and bacterial contamination during production

16.10 When dry materials and products are used in production, special precautions should be taken to prevent the generation and dissemination of dust. Provision should be made for proper air control (e.g. supply and extraction of air of suitable quality).

16.11 Contamination of a starting material or of a product by another material or product must be avoided. This risk of accidental cross-contamination arises from the uncontrolled release of dust, gases, particles, vapours, sprays or organisms from materials and products in process, from residues on equipment, from intruding insects, and from operators' clothing, skin, etc. The significance of this risk varies with the type of contaminant and of the product being contaminated. Among the most hazardous contaminants are highly sensitizing materials, biological preparations such as living organisms, certain hormones, cytotoxic substances, and other highly active materials. Products in which contamination is likely to be most significant are those administered by injection or applied to open wounds and those given in large doses and/or over a long time.

16.12 Cross-contamination should be avoided by taking appropriate technical or organizational measures, for example:

- (a) carrying out production in dedicated and self-contained areas (which may be required for products such as penicillins, live vaccines, live bacterial preparations and certain other biologicals);
- (b) conducting campaign production (separation in time) followed by appropriate cleaning in accordance with a validated cleaning procedure;



## QUALITY ASSURANCE OF PHARMACEUTICALS

- (c) providing appropriately designed airlocks, pressure differentials, and air supply and extraction systems;
- (d) minimizing the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;
- (e) wearing protective clothing where products or materials are handled;
- (f) using cleaning and decontamination procedures of known effectiveness;
- (g) using a “closed system” in production;
- (h) testing for residues;
- (i) using cleanliness status labels on equipment.

16.13 Measures to prevent cross-contamination and their effectiveness should be checked periodically according to standard operating procedures.

16.14 Production areas where susceptible products are processed should undergo periodic environmental monitoring (e.g. for microbiological monitoring and particulate matter where appropriate).

### Processing operations

16.15 Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues, labels or documents not required for the current operation.

16.16 Any necessary in-process controls and environmental controls should be carried out and recorded.

16.17 Means should be instituted of indicating failures of equipment or of services (e.g. water, gas) to equipment. Defective equipment should be withdrawn from use until the defect has been rectified. After use, production equipment should be cleaned without delay according to detailed written procedures and stored under clean and dry conditions in a separate area or in a manner that will prevent contamination.

16.18 Time limits for storage of equipment after cleaning and before use should be stated and based on data.

16.19 Containers for filling should be cleaned before filling. Attention should be given to avoiding and removing any contaminants such as glass fragments and metal particles.

16.20 Any significant deviation from the expected yield should be recorded and investigated.

16.21 Checks should be carried out to ensure that pipelines and other pieces of equipment used for the transportation of products from one area to another are connected in a correct manner.



## MAIN PRINCIPLES FOR PHARMACEUTICAL PRODUCTS

16.22 Pipes used for conveying distilled or deionized water and, where appropriate, other water pipes should be sanitized and stored according to written procedures that detail the action limits for microbiological contamination and the measures to be taken.

16.23 Measuring, weighing, recording, and control equipment and instruments should be serviced and calibrated at prespecified intervals and records maintained. To ensure satisfactory functioning, instruments should be checked daily or prior to use for performing analytical tests. The date of calibration and servicing and the date when recalibration is due should be clearly indicated, preferably on a label attached to the instrument.

16.24 Repair and maintenance operations should not present any hazard to the quality of the products.

### Packaging operations

16.25 When the programme for packaging operations is being set up, particular attention should be given to minimizing the risk of cross-contamination, mix-ups or substitutions. Different products should not be packaged in close proximity unless there is physical segregation or an alternative system that will provide equal assurance.

16.26 Before packaging operations are begun, steps should be taken to ensure that the work area, packaging lines, printing machines and other equipment are clean and free from any products, materials or documents used previously and which are not required for the current operation. The line clearance should be performed according to an appropriate procedure and checklist, and recorded.

16.27 The name and batch number of the product being handled should be displayed at each packaging station or line.

16.28 Normally, filling and sealing should be followed as quickly as possible by labelling. If labelling is delayed, appropriate procedures should be applied to ensure that no mix-ups or mislabelling can occur.

16.29 The correct performance of any printing (e.g. of code numbers or expiry dates) done separately or in the course of the packaging should be checked and recorded. Attention should be paid to printing by hand, which should be rechecked at regular intervals.

16.30 Special care should be taken when cut labels are used and when overprinting is carried out off-line, and in hand-packaging operations. Roll-feed labels are normally preferable to cut labels in helping to avoid mix-ups. On-line verification of all labels by automated electronic means can be helpful in preventing mix-ups, but checks should be made to ensure that any electronic code



## QUALITY ASSURANCE OF PHARMACEUTICALS

readers, label counters, or similar devices are operating correctly. When labels are attached manually, in-process control checks should be performed more frequently.

16.31 Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing.

16.32 Regular on-line control of the product during packaging should include at least checks on:

- (a) the general appearance of the packages;
- (b) whether the packages are complete;
- (c) whether the correct products and packaging materials are used;
- (d) whether any overprinting is correct;
- (e) the correct functioning of line monitors.

Samples taken away from the packaging line should not be returned.

16.33 Products that have been involved in an unusual event during packaging should be reintroduced into the process only after special inspection, investigation and approval by authorized personnel. A detailed record should be kept of this operation.

16.34 Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced should be investigated, satisfactorily accounted for, and recorded before release.

16.35 Upon completion of a packaging operation, any unused batch-coded packaging materials should be destroyed and the destruction recorded. A documented procedure requiring checks to be performed before returning unused materials should be followed if uncoded printed materials are returned to stock.

## 17. Good practices in quality control

17.1 Quality control is the part of GMP concerned with sampling, specifications and testing, and with the organization, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory. Quality control is not confined to laboratory operations but must be involved in all decisions concerning the quality of the product.

17.2 The independence of quality control from production is considered fundamental.

17.3 Each manufacturer (the holder of a manufacturing authorization) should have a quality control function. The quality control function should be inde-



## MAIN PRINCIPLES FOR PHARMACEUTICAL PRODUCTS

pendent of other departments and under the authority of a person with appropriate qualifications and experience, who has one or several control laboratories at his or her disposal. Adequate resources must be available to ensure that all the quality control arrangements are effectively and reliably carried out. The basic requirements for quality control are as follows:

- (a) adequate facilities, trained personnel and approved procedures must be available for sampling, inspecting, and testing starting materials, packaging materials, and intermediate, bulk, and finished products, and where appropriate for monitoring environmental conditions for GMP purposes;
- (b) samples of starting materials, packaging materials, intermediate products, bulk products and finished products must be taken by methods and personnel approved of by the quality control department;
- (c) qualification and validation must be performed;
- (d) records must be made (manually and/or by recording instruments) demonstrating that all the required sampling, inspecting and testing procedures have actually been carried out and that any deviations have been fully recorded and investigated;
- (e) the finished products must contain ingredients complying with the qualitative and quantitative composition of the product described in the marketing authorization; the ingredients must be of the required purity, in their proper container and correctly labelled;
- (f) records must be made of the results of inspecting and testing the materials and intermediate, bulk and finished products against specifications; product assessment must include a review and evaluation of the relevant production documentation and an assessment of deviations from specified procedures;
- (g) no batch of product is to be released for sale or supply prior to certification by the authorized person(s) that it is in accordance with the requirements of the marketing authorization. In certain countries, by law, the batch release is a task of the authorized person from production together with the authorized person from quality control;
- (h) sufficient samples of starting materials and products must be retained to permit future examination of the product if necessary; the retained product must be kept in its final pack unless the pack is exceptionally large.

17.4 Quality control as a whole will also have other duties, such as to establish, validate and implement all quality control procedures, to evaluate, maintain, and store the reference standards for substances, to ensure the correct labelling of containers of materials and products, to ensure that the stability of the active pharmaceutical ingredients and products is monitored, to participate in the investigation of complaints related to the quality of the product, and to participate in environmental monitoring. All these operations should be carried out in accordance with written procedures and, where necessary, recorded.





## QUALITY ASSURANCE OF PHARMACEUTICALS

17.5 Assessment of finished products should embrace all relevant factors, including the production conditions, the results of in-process testing, the manufacturing (including packaging) documentation, compliance with the specification for the finished product, and an examination of the finished pack.

17.6 Quality control personnel must have access to production areas for sampling and investigation as appropriate.

### Control of starting materials and intermediate, bulk and finished products

17.7 All tests should follow the instructions given in the relevant written test procedure for each material or product. The result should be checked by the supervisor before the material or product is released or rejected.

17.8 Samples should be representative of the batches of material from which they are taken in accordance with the approved written procedure.

17.9 Sampling should be carried out so as to avoid contamination or other adverse effects on quality. The containers that have been sampled should be marked accordingly and carefully resealed after sampling.

17.10 Care should be taken during sampling to guard against contamination or mix-up of, or by, the material being sampled. All sampling equipment that comes into contact with the material should be clean. Some particularly hazardous or potent materials may require special precautions.

17.11 Sampling equipment should be cleaned and, if necessary, sterilized before and after each use and stored separately from other laboratory equipment.

17.12 Each sample container should bear a label indicating:

- (a) the name of the sampled material;
- (b) the batch or lot number;
- (c) the number of the container from which the sample has been taken;
- (d) the number of the sample;
- (e) the signature of the person who has taken the sample;
- (f) the date of sampling.

17.13 Out-of-specification results obtained during testing of materials or products should be investigated in accordance with an approved procedure. Records should be maintained.





## Test requirements

### ***Starting and packaging materials***

17.14 Before releasing a starting or packaging material for use, the quality control manager should ensure that the materials have been tested for conformity with specifications for identity, strength, purity and other quality parameters.

17.15 An identity test should be conducted on a sample from each container of starting material (see also section 14.14).

17.16 Each batch (lot) of printed packaging materials must be examined following receipt.

17.17 In lieu of testing by the manufacturer, a certificate of analysis may be accepted from the supplier, provided that the manufacturer establishes the reliability of the supplier's analysis through appropriate periodic validation of the supplier's test results (see sections 8.8 and 8.9) and through on-site audits of the supplier's capabilities. (This does not affect section 17.15). Certificates must be originals (not photocopies) or otherwise have their authenticity assured. Certificates must contain at least the following information (6):

- (a) identification (name and address) of the issuing supplier;
- (b) signature of the competent official, and statement of his or her qualifications;
- (c) the name of the material tested;
- (d) the batch number of the material tested;
- (e) the specifications and methods used;
- (f) the test results obtained;
- (g) the date of testing.

### ***In-process control***

17.18 In-process control records should be maintained and form a part of the batch records (see section 15.25).

### ***Finished products***

17.19 For each batch of drug product, there should be an appropriate laboratory determination of satisfactory conformity to its finished product specification prior to release.

17.20 Products failing to meet the established specifications or any other relevant quality criteria should be rejected.



### Batch record review

17.21 Production and quality control records should be reviewed as part of the approval process of batch release. Any divergence or failure of a batch to meet its specifications should be thoroughly investigated. The investigation should, if necessary, extend to other batches of the same product and other products that may have been associated with the specific failure or discrepancy. A written record of the investigation should be made and should include the conclusion and follow-up action.

17.22 Retention samples from each batch of finished product should be kept for at least one year after the expiry date. Finished products should usually be kept in their final packaging and stored under the recommended conditions. If exceptionally large packages are produced, smaller samples might be stored in appropriate containers. Samples of active starting materials should be retained for at least one year beyond the expiry date of the corresponding finished product. Other starting materials (other than solvents, gases, and water) should be retained for a minimum of two years if their stability allows. Retention samples of materials and products should be of a size sufficient to permit at least two full re-examinations.

### Stability studies

17.23 Quality control should evaluate the quality and stability of finished pharmaceutical products and, when necessary, of starting materials and intermediate products.

17.24 Quality control should establish expiry dates and shelf-life specifications on the basis of stability tests related to storage conditions.

17.25 A written programme for ongoing stability determination should be developed and implemented to include elements such as:

- (a) a complete description of the drug involved in the study;
- (b) the complete set of testing parameters and methods, describing all tests for potency, purity, and physical characteristics and documented evidence that these tests indicate stability;
- (c) provision for the inclusion of a sufficient number of batches;
- (d) the testing schedule for each drug;
- (e) provision for special storage conditions;
- (f) provision for adequate sample retention;
- (g) a summary of all the data generated, including the evaluation and the conclusions of the study.

17.26 Stability should be determined prior to marketing and following any significant changes in processes, equipment, packaging materials, etc.



## References

1. Good Manufacturing Practices for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Twenty-second report*. Geneva, World Health Organization, 1992 Annex 1 (WHO Technical Report Series, No. 823).
2. Validation of analytical procedures used in the examination of pharmaceutical materials. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report*. Geneva, World Health Organization, 1992: Annex 5 (WHO Technical Report Series, No. 823).
3. *Good manufacturing practice for medicinal products in the European Community*. Brussels, Commission of the European Communities, 1992.
4. Pharmaceutical Inspection Convention, Pharmaceutical Inspection Co-operation Scheme (PIC/S). In: *Guide to good manufacturing practice for medicinal plants*, Geneva, PIC/S Secretariat, 2000.
5. *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Volume 2. Good manufacturing practices and inspection*. Geneva, World Health Organization, 1999.
6. Model certificate of analysis. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report*. Geneva, World Health Organization, 2002, Annex 10 (WHO Technical Report Series, No. 902).



# 2.

## WHO good manufacturing practices: starting materials

### Active pharmaceutical ingredients (bulk drug substances)<sup>1,2</sup>

Explanation	58
General considerations	58
Personnel	59
Premises	60
Equipment	60
Sanitation	61
Documentation	61
Retention of records and reference samples	63
Production	63

### Explanation

Since there are fundamental distinctions between the production of bulk active pharmaceutical ingredients and the formulation of finished pharmaceutical products, the strict application of GMP as set forth in the main part of this guide is not always practical or necessary. The present supplementary guidelines outline procedures and practices that manufacturers should employ to ensure that the methods, facilities, and controls used for the production of active pharmaceutical ingredients are operated or managed so that such products have the quality and purity appropriate for their use in finished pharmaceutical products.

### General considerations

18.1 In the manufacture of active pharmaceutical ingredients, overall control is essential to ensure high quality. Haphazard operations cannot be permitted in the

<sup>1</sup> Good manufacturing practices for pharmaceutical products, Part Three, section 18. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report*, Geneva, World Health Organization, 1992: 72–79 (WHO Technical Report Series, No. 823). The original numbering has been retained.

<sup>2</sup> Parts One and Two, Part Three, section 17, and the Introductory note, General considerations and Glossary of Good manufacturing practices for pharmaceutical products are reproduced elsewhere in this volume (see pp. 6–13, 13–45, 46–53, 75–83, 103–117).



manufacture of substances that may be used to save life or to restore or promote health.

18.2 Recommended practices for the manufacture of active pharmaceutical ingredients are set out below. Adherence to these practices, complementing the various control tests carried out from the beginning to the end of the production cycle, will contribute substantially to the production of consistently uniform batches of high-quality active pharmaceutical ingredients.

18.3 The manufacturer must assume responsibility for the quality of the active pharmaceutical ingredients produced. The manufacturer alone can avoid mistakes and prevent mishaps by exercising adequate care in both production and control procedures. Full evidence of compliance with GMP should be given from the step from which the processes or the starting materials used have a critical influence on the quality of the active pharmaceutical ingredient. This step should be determined in each individual case by agreement between the competent authority and the manufacturer.

18.4 The good practices outlined below should be considered general guides; whenever necessary, they may be adapted to meet individual needs provided the established standards of quality of the active pharmaceutical ingredients are still achieved. The good practices are intended to apply to the manufacturing processes (including packaging and labelling) used in the production of active pharmaceutical ingredients.

18.5 Sometimes several firms cooperate in the production (including packaging and labelling) of an active pharmaceutical ingredient. It may also happen that a finished, packed, and labelled active pharmaceutical ingredient is repacked and/or relabelled and given a new designation. Since such procedures constitute part of a manufacturing operation, they should be subject to the relevant guidelines set out below.

18.6 The practices outlined below are intended to apply to active pharmaceutical ingredients for both human and veterinary preparations.

## Personnel

18.7 Each firm should employ personnel with the necessary qualifications and competence for the production and quality control of active pharmaceutical ingredients. There should be an adequate number of staff with appropriate education, technical knowledge, and practical experience related to the job they perform.

18.8 The firm should have a defined organization represented in a chart. Individual responsibilities should be laid down in written instructions, to ensure that there are no gaps or overlaps. The responsibilities placed on any one individual should not be so extensive as to incur any risk to quality.



## QUALITY ASSURANCE OF PHARMACEUTICALS

18.9 Staff at all levels should be adequately trained for the tasks and responsibilities assigned to them.

18.10 Measures should be taken to ensure that no person affected by a disease in a communicable form or having open lesions on the exposed surface of the body is engaged in any production step involving direct contact with the active pharmaceutical ingredients.

### Premises

18.11 Premises, including areas containing open tanks, should be of suitable construction. They should provide a suitable environment for manufacturing operations and should be adequately adapted to and of a sufficient size for their intended use. The premises should not contribute to actual or potential mix-ups or contamination of the active pharmaceutical ingredients. The arrangement should provide for a logical work flow.

18.12 For special purposes, such as the production of sterile products and of certain antibiotics, hormones, and cytostatic substances, separate specifically designed enclosed areas with completely separate air-handling systems should be provided.

18.13 To maintain hygienic working conditions, the premises should include facilities for changing clothes, washing, and toilet purposes as well as for eating, drinking, and smoking.

### Equipment

18.14 Manufacturing equipment should be designed, constructed, located, and maintained in such a way as to:

- (a) be suitable for its intended use;
- (b) facilitate thorough cleaning;
- (c) minimize the risk of contamination of products and containers during production; and
- (d) facilitate efficient and, if applicable, validated and reliable operation.

18.15 Production and testing equipment should be cleaned, sterilized when necessary, used, and maintained in accordance with specific written instructions. Before production of another product is started, multipurpose equipment used should be thoroughly cleaned and checked for cleanliness. Appropriate records of such procedures should be maintained.

18.16 If necessary, equipment used for production and testing should have been shown to be capable of carrying out the processes for which it is intended.



18.17 Process-monitoring systems should be available where necessary. Measuring, recording, and control equipment should be calibrated and checked at suitable intervals by appropriate methods. Appropriate records of such tests should be maintained.

18.18 Defective equipment should be labelled immediately as defective and repaired or removed as soon as possible. Technical maintenance and repair should be documented.

## Sanitation

18.19 Written sanitation programmes should be available. These should include validated cleaning procedures for premises and equipment, a quality standard for water, instructions for hygiene when manufacturing and handling goods, and instructions relating to the health, hygienic practices, and clothing of personnel and the disposal procedures for waste materials and unusable residues.

18.20 These programmes should be implemented; they should regularly be brought to the attention of the personnel involved and emphasized during continued staff training.

18.21 Protective garments and other protective items appropriate to the processes being carried out should be worn.

18.22 Eating, smoking, and unhygienic practices should not be permitted in manufacturing areas.

## Documentation

### Master formulae

18.23 Written instructions covering each stage of production, storage, and quality control should be available, and they should be updated whenever necessary.

18.24 There should be a master formula setting out in writing the starting materials and packaging materials (quality and quantity), as well as detailed production and quality control procedures for each active pharmaceutical ingredient. Wherever possible, the master formula should be prepared for standard batch sizes.

18.25 Competent persons experienced in production and quality control should be responsible for the content and distribution within the firm of instructions and master formulae. These should be duly signed and dated.

18.26 Outdated master formulae should be withdrawn but retained for reference. Copies of the master formula should be prepared in a manner that will eliminate any possibility of transcription error.



## QUALITY ASSURANCE OF PHARMACEUTICALS

18.27 In certain circumstances, for example in the first production runs following pilot development, the master formula might need to be amended. Any amendments must be formally authorized and signed by competent person(s). The amended document should be replaced at the earliest opportunity by a newly prepared master formula.

### Batch documentation

18.28 A batch manufacturing record should be completed during the production of each batch of intermediate products and of active pharmaceutical ingredients. It should contain the relevant parts of the master formula and should include the following:

- (a) the name of the product (if applicable, the International Non-proprietary Name) or stage and the size and number of the batch;
- (b) the dates of the different stages of production;
- (c) production details, including reference to the main equipment used and yields;
- (d) the batch or reference number (or analytical control number), if any, of starting materials used in the production;
- (e) a record of the in-process controls followed and the results obtained;
- (f) details of, and signed authorization for, any deviation from the master formula (any unplanned deviation being subject to investigation in relation to product quality);
- (g) any recovered materials, and procedures applied;
- (h) the initials of the operators and signature of the person responsible for the production operations and the date of signature;
- (i) all analytical records relating to the batch, or a reference that will permit their retrieval;
- (j) a decision for the release or rejection of the batch with the date and signature of the person responsible for the decision;
- (k) the production record review (see section 16.15).

18.29 Where circumstances require the use of contract production and control facilities, this fact should be stated in the batch record.

18.30 Data may be recorded by electronic data-processing systems or by photographic or other reliable means. Master formulae and detailed standard operating procedures relating to the system in use should be available and the accuracy of the records should be checked. If documentation is handled by electronic data-processing methods, only authorized persons should be able to enter or modify data in the computer, and there should be a record of changes and deletions; access should be restricted by passwords or other means, and the entry of critical data should be independently checked. Batch records electronically stored should be protected by back-up transfer on magnetic tape,





microfilm, paper print-outs, or other means. It is particularly important that, during the period of retention, the data are readily available.

## Retention of records and reference samples

18.31 Records should be kept in such a way that activities concerning the production and quality control of active pharmaceutical ingredients are traceable.

18.32 Records and reference samples of the active pharmaceutical ingredients, and where necessary of intermediate products, should be retained at least one year beyond the expiry date of the finished product or for a specified period if there is no expiry date.

## Production

### Processing procedures

18.33 Processing should be carried out in accordance with the master formula.

18.34 Steps that are critical for the quality of the active pharmaceutical ingredient should be defined and the procedures applied should be validated.

18.35 Processing should be supervised and performed by competent persons.

18.36 During processing, vessels, containers, and significant equipment should be unambiguously labelled or identified with the name of the product and the batch number.

18.37 Information on the daily activities in each processing department should be available in addition to the batch documentation.

### Starting materials

18.38 Starting materials should be received, quarantined, sampled, identified, examined for compliance with established specifications, released or rejected, stored, labelled, and dispensed in accordance with written instructions.

18.39 Some starting materials may not be tested for compliance because of the hazards involved (e.g., phosphorus pentachloride and dimethyl sulfate). This is acceptable when a batch certificate of analysis is available from the vendor and when there is a reason based on safety or other valid considerations.

### Intermediate products

18.40 Intermediate products should, where necessary, be tested in accordance with the specifications and should be conspicuously labelled/identified and properly stored.



## QUALITY ASSURANCE OF PHARMACEUTICALS

### Active pharmaceutical ingredients

18.41 Each batch of finished active pharmaceutical ingredient must meet established specifications for quality, purity, identity, and potency, including, where applicable, specifications for tests and limits for residues of solvents and other reactants.

18.42 For the production of sterile active pharmaceutical ingredients, section 17 (“Sterile pharmaceutical products”) may be applicable to the steps at which the process may have a critical influence on the quality attributes of the finished pharmaceutical product.

### Packaging

18.43 Care should be exercised when packaging materials are selected for active pharmaceutical ingredients. The materials should have no detrimental effect on the substance, and should give adequate protection against external influences and potential contamination. Suitable written specifications should be available.

18.44 Attention should be directed at all stages to the prevention of packaging errors. Sound procedures must be employed to protect the quality of the product when it is packaged and to ensure that the correct labels are applied to the containers.

18.45 The containers should be conspicuously marked with the following information:

- (a) the name of the product;
- (b) its quality, if specified;
- (c) the batch number;
- (d) the expiry or retest date, if specified;
- (e) warnings, if required;
- (f) storage conditions, if specified; and
- (g) the names of the manufacturer and the supplier.

### Quality control

18.46 Every manufacturer should have an independent quality control unit, the head of which is directly responsible to the management of the firm. The principal duties of the quality control unit are listed below.

- (a) It should approve:
  - (i) specifications and testing methods for starting materials, intermediate products and, if required, packaging materials and active pharmaceutical ingredients;



## STARTING MATERIALS

- (ii) sampling procedures;
  - (iii) instructions regarding sanitation and hygiene;
  - (iv) reprocessing procedures for rejected batches or recovered materials;
  - (v) other instructions related to the quality of the product.
- (b) It should be responsible for the release or rejection of starting materials, active pharmaceutical ingredients, packaging materials, and, if required, intermediate products.
- (c) It should ensure that the stability of active pharmaceutical ingredients is monitored.
- (d) It should be responsible for the investigation of complaints related to the quality of active pharmaceutical ingredients.

18.47 Every manufacturer should have access to a control laboratory. The laboratory should be staffed and fully equipped for performing all quality control tests required. The tests should be performed in accordance with written and validated procedures. Instruments should be calibrated at suitable intervals and reagents should be of appropriate quality.

18.48 Where circumstances require the use of outside laboratories, this fact should be stated in the analytical records.

### Stability studies

18.49 A written stability-testing programme should be established for active pharmaceutical ingredients. Stability-indicating methods should be used.

18.50 Samples should be stored in suitable containers and in simulated market containers at room temperature or the recommended temperature and under stress conditions.

18.51 Expiry dates do not usually need to be set for active pharmaceutical ingredients. If testing does not indicate a reasonable shelf-life, e.g., two years or more under anticipated storage conditions, then the product can be labelled with an appropriate arbitrary expiry date and should be retested on or before that date.

### Self-inspection and quality audits

18.52 In order to maintain strict adherence to GMP and to all manufacturing procedures and prescribed controls, it is advisable for a firm to designate an expert or a team of experts to conduct regular independent inspections of its overall production and control procedures. Such experts should be as independent as possible in their inspection of production and control procedures.

18.53 Self-inspections and audits (see section 9) should be recorded.



## QUALITY ASSURANCE OF PHARMACEUTICALS

### Storage

18.54 Active pharmaceutical ingredients should be stored under conditions established by the manufacturer on the basis of stability studies.

18.55 Records should be maintained on the distribution of each batch of an active pharmaceutical ingredient in order to facilitate the recall of the batch if necessary, according to written procedures.

### Complaints and defects

18.56 The manufacturer should maintain written instructions for dealing with complaints and defects concerning the quality of active pharmaceutical ingredients.

18.57 All necessary action should be taken promptly, the complaints thoroughly investigated, and all facts recorded.

18.58 The manufacturer should have a system to allow review of all products that may have been affected by a repetitive error or a failure in the procedures of the firm.

### Rejected materials

18.59 The manufacturer should maintain written instructions concerning the handling of rejected materials, whether starting materials, intermediate products, packaging materials, or active pharmaceutical ingredients. Rejected materials should be conspicuously identified as such and stored in a controlled manner pending destruction, reprocessing, or return to the supplier.

## Pharmaceutical excipients<sup>1</sup>

1. General considerations	67
2. Glossary	70
3. Self-inspection and quality audits	71
4. Equipment	72
4.1 Use of equipment	72
4.2 Cleaning programme	72
4.2.1 Detailed cleaning procedure	73
4.2.2 Sampling plan	73
4.2.3 Analytical methods/cleaning limits	73

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<sup>1</sup> Good manufacturing practices: supplementary guidelines for the manufacture of pharmaceutical excipients. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fifth report.* Geneva, World Health Organization, 1999, Annex 5 (WHO Technical Report Series, No. 885).



5. Materials	73
5.1 General	73
5.2 Starting materials	74
5.3 Rejected and recovered materials	74
5.4 Returned excipients	75
5.5 Storage practices	75
6. Documentation	75
6.1 General	75
6.2 Specifications	76
6.3 Batch production records	76
6.4 Other documents	77
7. Good practices in production and quality control	77
7.1 Change control and process validation	77
7.2 Good practices in production	78
7.2.1 Prevention of cross-contamination	78
7.2.2 In-process blending/mixing	79
7.2.3 Control of microbial contamination	80
7.2.4 Water systems/water quality	81
7.2.5 Packaging operations	82
7.2.6 Delivery	82
7.3 Good practices in quality control	82
7.3.1 General	82
7.3.2 Control of starting materials	82
7.3.3 In-process testing	83
7.3.4 Quality records and retention samples	83
7.3.5 Stability studies	83
7.3.6 Expiry/re-evaluation dating	84
7.3.7 Calibration of measuring and test equipment	84

## 1. General considerations

These guidelines, which focus on aspects of good manufacturing practices (GMP) specific for pharmaceutical excipients, supplement the general GMP guidelines for pharmaceutical products published by WHO.<sup>1</sup> They also incorporate some of the concepts for quality management systems determined by the International Organization for Standardization (ISO).

Excipients significantly affect the finished product quality, in some cases making up almost the entire formulation. Many pharmaceutical excipients are

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<sup>1</sup> Good manufacturing practices for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Thirty-second report*. Geneva, World Health Organization, 1992, Annex 1 (WHO Technical Report Series, No. 823). In this volume, see pp. 6–13, 13–45, 46–53, 75–83, 103–117.



## QUALITY ASSURANCE OF PHARMACEUTICALS

used in much greater quantities in other industries, such as the food, cosmetic or industrial chemical industry. Consistency and rigour of product specifications may not be as critical in these industries as they are for pharmaceuticals, and many of the excipients used are highly variable. Therefore, a programme must be in place which will monitor these excipients and provide the necessary assurance that they meet the quality parameters for pharmaceutical manufacturing processes. The purpose of this document is to lay out some criteria which may be used to achieve this level of assurance.

The formulator of the finished dosage form is highly dependent on the excipient manufacturer to provide bulk substances that are uniform in chemical and physical characteristics. This is particularly important in the product approval process, where bioequivalence comparisons are made between clinical bioequivalence (“biobatch”) production and commercial scale-up batches. To provide adequate assurance of drug product performance *in vivo*, the excipient used to manufacture commercial batches should not differ significantly from that used in biobatches. Where significant differences may be expected, additional testing by the finished dosage manufacturer may be required to establish the bioequivalence of the finished product. It remains equally important to ensure that the bioequivalence of subsequent, post-approval commercial batches of drug products is not adversely affected over time.

In general, excipients are used as purchased, with no further refinement or purification. Consequently, impurities present in the excipient will be carried over to the finished dosage form. While dosage form manufacturers may have a limited control over excipient quality (i.e. by obtaining certificates of analysis and testing representative samples), the excipient manufacturer has greater control over physical characteristics, quality, and the presence of trace-level impurities in the excipient. The excipient manufacturer should perform periodic performance trend analyses of processes, and the purchaser of the material should also maintain a trend analysis of all testing done on the excipient upon receipt.

In the manufacture of excipients, the environmental conditions, equipment and operational techniques employed reflect the chemical industry rather than the finished drug manufacturing industry. In some processes chemical and biochemical mechanisms have not been fully characterized; therefore, the methods and procedures for materials accountability will often differ from those applicable to the manufacture of finished dosage forms. Many chemical processes are performed in closed systems that tend to provide protection against contamination, even when the reaction vessels are not enclosed in buildings. However, this does not preclude the introduction of contaminants from equipment, materials used to protect equipment, corrosion, cleaning and personnel.

Some excipient manufacturing processes may require observance of GMP applicable to finished drug products or bulk active ingredients because of the excipient’s intended use. However, such observance is neither feasible nor necessary in many processes, particularly during the early processing steps. The



requirements increase as the process progresses. At some logical processing step, usually well before the final finishing operation, appropriate GMP should be imposed and maintained throughout the remainder of the process. To determine the processing step at which these GMP should be implemented, good judgement and a thorough knowledge of the process are required. A detailed process flow should identify the unit operations, equipment used, stages at which various substances are added, key steps in the process, critical parameters (time, temperature, pressure, etc.) and monitoring points.

An excipient manufacturer should be able to identify critical or key points in the process where selective intermediate sampling and testing is necessary in order to monitor process performance. Towards the end of the process, the records should be increasingly thorough.

Significant processing steps, required to produce an excipient that meets the established physical and chemical criteria, should be identified by the excipient manufacturer. These steps can involve a number of unit operations or unit processes. Unit operations include physical processing steps involving energy transfer where there is no chemical change of the molecule. Unit processes are those processing steps where the molecule undergoes a chemical change.

Significant processing steps include but are not limited to the following:

- Phase changes involving either the desired molecule, a solvent, inert carrier or vehicle (e.g. dissolution, crystallization, evaporation, drying, sublimation, distillation or absorption).
- Phase separation (e.g. filtration or centrifugation).
- Chemical changes involving the desired molecule (e.g. removal or addition of water of hydration, acetylation, formation of a salt).
- Adjustments of the solution containing the molecule (e.g. adjustment of pH).
- Precision measurement of added excipient components, in-process solutions, recycled materials (e.g. weighing, volumetric measuring).
- Mixing of multiple components.
- Changes that occur in surface area, particle size or batch uniformity (e.g. milling, agglomeration, blending).

Automated process controls and processing equipment are more likely to be used in an excipient plant than in a plant manufacturing finished dosage forms. Use of automated equipment is appropriate when adequate inspection, calibration, and maintenance procedures are performed. Production equipment and operations will vary depending on the type of excipient being produced, the scale of production, and the type of operation (i.e. batch versus continuous).

ISO “certification” for excipient manufacture is increasingly being required by final dosage formulators in the USA, Europe and Japan. Compliance to the International Standards of ISO 9000 series, in particular to ISO 9002, can confer greater acceptability of a supplier’s excipients in world markets. There is additional value to applying the principles of ISO 9000 to excipient manufacture, since quality system measures enhance GMP. Such ISO considerations as con-



## QUALITY ASSURANCE OF PHARMACEUTICALS

formance to specific customer requirements, purchase of raw materials and statistical techniques benefit both the excipient customer and the manufacturer, and strengthen the relationship between the two.

It is therefore recommended that excipient manufacturers establish and implement a formal company-wide quality policy. Management should be committed to this policy and should appoint appropriate company personnel to be responsible for coordination and implementation of the quality system. Management should participate in the development of the company's quality policy and provide the resources necessary for development, maintenance and periodic review of such a policy and quality system. Any significant changes in the processes should be validated with respect to excipient performance. It is recommended that all pharmaceutical manufacturers and also local agents should be informed of these changes. Ideally, excipient manufacturers should not subcontract any part of their process without the explicit knowledge of the pharmaceutical manufacturer.

Safe handling instructions should be provided by the excipient manufacturer to ensure that the purchaser is adequately equipped to handle the material. This should include information on the material's toxicity and the measurements to be taken upon accidental exposure. The equipment requirements for proper handling of the material should also be established.

## 2. Glossary

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

### *commingling*

The blending of carry-over material from one grade of an excipient with another, usually due to a continuous process.

### *drug master file*<sup>1</sup>

Detailed information concerning a specific facility, process or product submitted to the drug regulatory authority, intended for incorporation into the application for marketing authorization.

### *model product*

A product which simulates a group of similar products.

### *mother liquor*

A concentrated solution from which the product is obtained by evaporation, freezing, and/or crystallization.

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<sup>1</sup> This term appears to be specific to United States regulations.





*pharmaceutical excipients*

Substances, other than the active ingredient, which have been appropriately evaluated for safety and are included in a drug delivery system to:

- aid in the processing of the drug delivery system during its manufacture;
- protect, support or enhance stability, bioavailability, or patient acceptability;
- assist in product identification; or
- enhance any other attribute of the overall safety and effectiveness of the drug during storage or use.

### 3. Self-inspection and quality audits

An inspection team consisting of appropriate personnel (e.g. auditors, engineers, laboratory analysts, purchasing agents, computer experts) should participate in inspections. The operational limitations and validation of the critical processing steps of a production process should be examined, to make sure that the manufacturer is taking adequate steps to check that the process works consistently.

The excipient's end use should be identified and considered during inspection of excipient manufacturers. It is particularly important to know whether the excipient is a direct or indirect component of a drug dosage form; whether the excipient will be used in the preparation of a sterile dosage form; and whether the excipient is presented as pyrogen/endotoxin free. The excipient manufacturer is responsible for ensuring that excipients are pyrogen free if the manufacturer makes such a representation in specifications, labels or a drug master file.

A good starting point for an excipient plant inspection is a review of the following areas:

- Non-conformance, such as the rejection of a batch not complying with specifications, return of a product by a customer, or recall of a product. The cause of non-conformance should have been determined by the manufacturer, a report of the investigation prepared, and subsequent corrective action initiated and documented. Records and documents should be reviewed to ensure that such non-conformance is not the result of a poorly developed or inconsistent process.
- Complaint files. Customers may report some aspects of product attributes that are not entirely suitable for their use. These may be caused by impurities or inconsistencies in the excipient manufacturing process.
- Change control documentation.
- Master formula and batch production records. Frequent revisions may reveal problems in the production process.
- Specifications for the presence of unreacted intermediates and solvent residues in the finished excipient.
- Storage areas for rejected products.



## QUALITY ASSURANCE OF PHARMACEUTICALS

In evaluating the adequacy of measures taken to preclude contamination of materials in the process, it is appropriate to consider the following factors:

- Type of system (e.g. open or closed). “Closed” systems in chemical plants are often not closed when they are being charged and/or when the final product is being removed. Also, the same reaction vessels are sometimes used for different reactions.
- Form of the material (e.g. wet or dry).
- Stage of processing and use of the equipment and/or area (e.g. multipurpose or dedicated).

Other factors that should be considered in evaluating an excipient plant are:

- Degree of exposure of the material to adverse environmental conditions.
- Relative ease and thoroughness of clean-up.
- Sterile versus non-sterile operations.

## 4. Equipment

### 4.1 Use of equipment

Many excipients are produced using multipurpose equipment. Fermentation tanks, reactors, driers, grinders, centrifuges and other pieces of equipment are readily used or adapted for a variety of products. With few exceptions such multiple usage is satisfactory provided the equipment can be adequately cleaned according to written procedures. Equipment that contains tarry or gummy residues that cannot be removed easily should be dedicated for use with these products only.

Some fermentation tanks, reaction vessels, and other equipment are not situated within a building and a considerable amount of processing occurs out of doors. Such processing is acceptable provided it occurs in a closed system.

Where temperature control is important, temperature recording devices should be used, with recording charts kept as part of the batch record.

### 4.2 Cleaning programme

Where multipurpose equipment is in use, it is important to be able to determine previous usage when investigating cross-contamination or the possibility of such contamination. An equipment cleaning and use log, while desirable and perhaps preferable, is not the only method of determining prior use. Any documentation system which clearly identifies the previous batch and shows that the equipment was cleaned is acceptable. For operations where multiple grades of the same chemical entity are processed, there must be documentation showing that the previous grade was removed. Validation data must exist to prove acceptability of the cleaning procedure.



Cleaning of multiple-use equipment should be confirmed. The manufacturer should determine the effectiveness of the cleaning procedure for each excipient or intermediate chemical used in that particular piece of equipment. The validation data required depend on the types of materials being made in the multiple-use equipment and the impact of trace contaminants on drug safety and performance. Validation data should verify that the cleaning process has removed residues to an acceptable level.

As an example, an equipment cleaning programme may include, but is not limited to, the following:

#### **4.2.1 Detailed cleaning procedure**

There should be a written equipment cleaning procedure that provides details of what should be done and which cleaning materials should be used. Some manufacturers list the specific solvents used for each excipient and intermediate.

#### **4.2.2 Sampling plan**

There should be some periodic testing after cleaning, to ensure that the surface has been cleaned to the required level. One common method is to analyse the final rinse water or solvent for the presence of the substance last used in that piece of equipment. In some cases, visual inspections may be appropriate. A specific analytical method to determinate residual substances may not always be available, but is preferred. The need for an analytical method would be based on the potential adverse effect on product quality, performance or safety. When safety is a concern, there should be a specific analytical determination for a residual substance.

#### **4.2.3 Analytical methods/cleaning limits**

The toxicity of the residual materials should be considered when deciding on the appropriate analytical method and the residual cleaning limits. The residue limits established for each piece of apparatus should be practical, achievable and verifiable. The manufacturer should be able to show, with supporting data, that the residual level permitted is scientifically based. Another factor to consider is the possible non-uniformity of the residue. The level of residue found by random sampling, such as taking a swab from a limited area on a piece of equipment, does not necessarily represent the highest level of contamination.

## **5. Materials**

### **5.1 General**

In the case of labile products that may be sensitive to environmental factors such as air, light, water, heat or cold, appropriate manufacturing and storage conditions must be used to ensure product quality throughout the process.



## 5.2 Starting materials

The excipient manufacturer should verify that the supplier of starting materials and components can meet the agreed-upon requirements. This may require periodic audits of the vendor's plant if necessary. Purchasing agreements should contain data clearly describing the product ordered including, where applicable, the following:

- The name, type, class, style, grade, item code numbers or other precise identification as appropriate.
- Drawings, process requirements, inspection instructions and other relevant technical data, including requirements for approval or verification of product, procedures, process equipment and personnel.

Starting materials, including solvents and recovered solvents, are sometimes stored in silos or other large containers, making precise separation of batches difficult. Usage of such materials should be demonstrated, via inventory or other records, with reasonable accuracy.

When purchased and recovered solvents are commingled, the suitability of the recovered solvent must be demonstrated through either validation or actual testing. The purchased materials should comply with existing specifications.

Outdoor storage of starting materials (e.g. acids, other corrosive substances, explosive materials) is acceptable if the containers give suitable protection to their contents, identifying labels remain legible and containers are adequately cleaned prior to opening and use.

## 5.3 Rejected and recovered materials

Any starting material, intermediate or finished excipient not complying with specifications must be clearly identified and segregated to prevent inadvertent use or release for sale. A record of non-compliance should be maintained. All cases of non-compliance should be investigated to identify the root cause.

These materials may be:

- reprocessed/reworked to meet the specified requirements;
- regraded for alternative applications; or
- rejected or scrapped.

Occasional reprocessing/reworking of an excipient may be acceptable. However, relying on the final testing only of the reprocessed excipient to demonstrate compliance to specification is not acceptable. The quality of the reprocessed material must be evaluated and documented showing adequate investigation and demonstrating that the reprocessed excipient is at least equivalent to other acceptable excipients. When reprocessing has to be done frequently, it may be an indication that the process, work instruction or training is inadequate and needs to be adjusted or reinforced.



## 5.4 Returned excipients

Returned excipients should be identified as such and kept. If the conditions under which the products have been stored and shipped or if the condition of the container itself casts doubt on the safety, quality or purity of the excipient, the product should be destroyed, unless thorough examination, testing, or other investigation shows that the product meets the appropriate predefined standards. If returned excipient containers are reused, all previous labelling should be removed or defaced. If the containers are used repeatedly solely for the same excipient, all previous batch numbers, or the entire label, should be removed or completely obliterated.

## 5.5 Storage practices

Pharmaceutical excipients should be stored under conditions established by the manufacturer on the basis of stability data. Records should be kept of the distribution of each batch of pharmaceutical excipient, to facilitate the recall of the batch if necessary, according to written procedures.

# 6. Documentation

## 6.1 General

The excipient manufacturer should have a system to cover all documents and data that relate to the requirements of the quality system. Documents, and subsequent changes to the documents, should be reviewed and approved by designated personnel before being issued to the appropriate areas identified in the documents. A record should be kept of where the documents are located.

The following minimal requirements for documentation should be applied:

- To assign a unique batch number to the excipient to be released and/or certified.
- To prepare a batch record.
- To demonstrate that the batch has been prepared under GMP conditions from the processing point at which excipient GMP have been applied.
- To demonstrate that the batch is homogeneous within the manufacturer's specifications. This does not require a final blending of continuous process material, if process controls can demonstrate compliance with specifications throughout the batch.
- To demonstrate that the batch has not been commingled with material from other batches for the purpose of either hiding or diluting an adulterated substance.
- To demonstrate that the batch has been sampled in accordance with a sampling plan that ensures a representative sample of the batch is taken.



## QUALITY ASSURANCE OF PHARMACEUTICALS

- To demonstrate that the batch has been analysed using scientifically established tests and methods designed to ensure that the product meets accepted standards and specifications for quality, identity and purity.
- To demonstrate that the batch has stability data to support the intended period of use; these data can be obtained from actual studies on the specific excipient or from applicable “model product” stability studies that can reasonably be expected to simulate the performance of the excipient.

### 6.2 Specifications

Starting material specifications should be organized to separate those tests that are routine from those that are performed infrequently or only for new suppliers. Relevant pharmacopoeial monographs, when available, provide a basis for the development of internal manufacturer’s specifications.

A positive identification test uniquely applicable to the excipients should be established through analytical technology, such as infrared spectrophotometry and chromatography.

It is important that manufacturers identify and set appropriate limits for impurities. These limits should be based upon appropriate toxicological data, or limits described in national compendial requirements. Manufacturing processes should be adequately controlled so that the impurities do not exceed such established specifications.

Many excipients are extracted from or purified by the use of organic solvents. These solvents are normally removed by drying the moist excipient. In view of the varying and sometimes unknown toxicity of solvents, it is important that excipient specifications include tests and limits for residues of solvents and other reactants.

Container specifications should be established for all excipients to assure consistency in protecting the product during transport from the excipient manufacturer to the pharmaceutical producer. The specifications should not only provide for containers that maintain the stability of the product, but should also meet requirements for protection during shipping, against insect infestation, during handling, etc.

### 6.3 Batch production records

Computer systems are increasingly used to initiate, monitor, adjust and otherwise control manufacturing processes. These operations may be accompanied by recording charts that show key parameters (e.g. temperature) at suitable intervals, or even continuously, throughout the process. In other cases, key measurements (e.g. pH) may be displayed temporarily on a monitor screen, but are not available in hard copy.

Records showing addition of ingredients, actual performance of operations by identifiable individuals, and other information usually seen in conventional records, may be missing. When computers and other sophisticated equipment are



employed, the emphasis must change from conventional, hand-written records to:

- systems and procedures that show the equipment and software is in fact performing as intended;
- checking and calibration of the equipment at appropriate intervals;
- retention of suitable back-up systems such as copies of the program and files, duplicate tapes or microfilm;
- assurance that changes in the program are made only by authorized personnel and that they are clearly documented and validated.

#### 6.4 Other documents

Shipping and storage requirements should be established to ensure that the product reaches the manufacturer with proper quality attributes. This should be mutually agreed upon between the vendor and the purchaser and established prior to transportation of product.

Written procedures should be established and followed for maintenance of the equipment. All maintenance activities performed must be recorded; this may be in the form of a log, computer data base or other appropriate documentation, as long as the system can identify who was responsible for performing each function.

### 7. Good practices in production and quality control

#### 7.1 Change control and process validation

Process changes may lead to changes in inherent product characteristics. Manufacturers should have a formal process change system in place, with written standard operating procedures covering such changes. Management of the change system should be assigned to an independent quality unit having responsibility and authority for final approval of process changes.

Manufacturers of excipients often produce laboratory or pilot batches. Scale-up to commercial production may involve several stages and data should be reviewed to demonstrate the adequacy of the scale-up process. Scale-up may introduce significant problems of consistency between batches. Pilot batches should serve as the basis for establishing in-process and finished product purity specifications.

Typically, manufacturers will generate reports that discuss the development and limitation of the manufacturing process. Summaries of such reports should be reviewed to determine if the plant is capable of producing the excipient. The reports serve as the basis for the validation of the manufacturing and control procedures, as well as the basic documentation to demonstrate that the process works consistently.



## QUALITY ASSURANCE OF PHARMACEUTICALS

A document comprising scale-up data and describing the process reactions, operating parameters, purifications, impurities and key tests needed for process control should be written. A retrospective analysis of historical data (through statistical data and process capability data analysis) as well as the previous documentation will provide a good basis for validation.

### 7.2 Good practices in production

#### **7.2.1 Prevention of cross-contamination**

Potential for cross-contamination should be considered in the design of the manufacturing process and facility. The degree to which cross-contamination should be minimized depends on the safety and intended use of the excipient.

The precautions taken to minimize cross-contamination should be appropriate to the conditions of the manufacturing facility and will take account of the range of materials manufactured. When the excipient product is initially recovered, it should be in a clean environment and not exposed to airborne contaminants, such as dust from other excipient or industrial chemicals. Typically, the damp product will be unloaded into clean, covered containers and transported for drying and other manipulations. These subsequent operations should be performed in separate areas or under controlled conditions because once dry, the excipient is more likely to contaminate its environment, including any surrounding products. The primary consideration is that the building and facilities should not contribute to an actual or potential contamination of the excipient.

The air handling systems at the site of manufacture should be designed to prevent cross-contamination. In dedicated areas processing the same excipient, it is permissible to recycle a portion of the exhaust air back into the same area. The adequacy of such a system of operation for multi-use areas, especially if several products are processed simultaneously, should be carefully analysed. In multi-use areas where several products are completely confined in closed vessels and piping systems, filtration of the supply air (combined fresh make-up air and recycled air) is acceptable if the conditions are consistent with other existing regulations (e.g. environmental, safety).

In those areas where the excipient is in a damp or moistened form, such as filter or centrifuge cake, and may be exposed to room air, filter efficiencies in the supply air system as low as 85% may be adequate. In those areas where one or more of the products is being processed in a dry form, such filtration may not be enough to prevent cross-contamination. In all cases, manufacturers should be able to demonstrate the adequacy of their air handling systems.

Excipient manufacturers should have a documented programme identifying all insecticides, pesticides, rodenticides and herbicides used at the site of manufacture. Adequate measures should be taken to prevent these agents contaminating the excipients.





### 7.2.2 In-process blending/mixing

Some processes require blending or mixing. Such in-process blending is acceptable provided it is adequately documented in batch production records. Examples include:

- Collection of multiple batches or continuous accumulation of batches with defined endpoint in a single holding tank (with a new batch number).
- Recycling material from one batch for further use in a subsequent batch.
- Repeated crystallizations of the same mother liquor for better yield of crystals.
- Collecting several centrifuge loads in a single drier/blender.

Incidental carry-over is another type of in-process mixing that frequently occurs. Examples include:

- Residue adhering to the wall of a micronizer used for milling the finished excipient.
- Residual layer of damp crystals remaining in a centrifuge bowl after discharge of the bulk of the crystals from a prior batch.
- Incomplete discharge of fluids, crystals or particles from a processing vessel upon transfer of the material to the next step in the process.

These residues are usually acceptable since clean-up between successive batches of the same excipient is not normally required during production. However, in the case of non-dedicated production units, complete cleaning procedures designed to prevent contamination that would alter the quality of the substance must be employed when changing from one excipient to another. Checking the effectiveness of these cleaning procedures may require the use of analytical testing for the substances involved.

In contrast to in-process blending and incidental carry-over discussed above, other blending operations should be directed towards achieving homogeneity of the finished excipient batch. Three areas in the processing of finished batches of an excipient which should be examined carefully and critically are:

- the final blending operation to produce the finished batch;
- the point in the process at which the batch number is assigned;
- the sampling procedure used to obtain the sample that is intended to be representative of the batch.

Blending of excipient batches to salvage adulterated material is not an acceptable practice.

Mother liquors containing recoverable amounts of excipients are frequently reused. Secondary recovery procedures for such excipients are acceptable, if the recovered excipient meets its specifications and if recovery procedures are indicated in batch production records. Secondary recovery procedures for



reactants and intermediates are acceptable provided that the recovered materials meet suitable specifications.

### **7.2.3 Control of microbial contamination**

The manufacture of sterile excipients for use in aseptic/sterile processing presents technical challenges. It is essential that adequately qualified and trained personnel be used to supervise and perform procedures associated with the manufacture of sterile excipients. The environment in which procedures are conducted, and the operators themselves, are significant potential sources of contamination in aseptic operations. Processes should be designed to minimize contact between excipient and the environment and operators. Those aseptic excipient operations which require considerable operator involvement must have adequate controls. Major potential problem areas include aseptic removal of the excipient from centrifuges, manual transfer to drying trays and mills, and the inability to sterilize the drier. Not all equipment currently in use can be sterilized.

The excipient manufacturer must document the cleaning of critical processing equipment such as centrifuges and driers. Any manipulation of sterile excipients after sterilization must be performed as a validated aseptic process. This is particularly important for those excipients which are not further sterilized prior to packaging into final containers. In some instances, the compendial monographs may specify that an excipient which does not meet parenteral grade standards must be labelled as not suitable for use in the preparation of injectable products.

Some manufacturers of non-sterile excipients use heat, gamma radiation and other methods to reduce the microbial burden. These methods are acceptable provided the manufacturer has shown that the product meets microbial requirements and that the process is under control within the manufacturer's specifications. Any procedure should be validated in accordance with recognized international standards to demonstrate that the process will produce the intended result. Post-production treatment of excipients should not be used as a substitute for attention to microbiological control during production.

A protected environment may be necessary to avoid microbial contamination or degradation caused by exposure to heat, air or light. The degree of protection required may vary depending on the stage of the process. Often, direct operator contact is involved in the unloading of centrifuge bags, transfer hoses (particularly those used to transfer powders), drying equipment and pumps, and equipment should be designed to minimize the possibility of contamination. The sanitary design of transfer and processing equipment should be evaluated. Those with moving parts should be assessed for the integrity of seals and other packing materials to avoid product contamination.

Special environments required by some processes must be monitored at all times to ensure product quality (e.g. inert atmosphere, protection from light). If interruptions in the special environment occur, adequate evidence must be



provided that they have not compromised the quality of the excipient. Such environmental concerns become increasingly important after purification of the excipient has been completed.

The environment to which the excipient may be exposed should be similar to that used in the manufacture of the final dosage form. This is especially true in the case of excipients intended for parenteral dosage forms. For example, controlled areas may need to be established along with appropriate air quality classifications. Such areas should be serviced by suitable air handling systems and there should be adequate environmental monitoring programmes. Any manipulation of sterile excipient after sterilization must be performed as an aseptic process, using Class 100 air<sup>1</sup> and other aseptic controls.

#### **7.2.4 Water systems/water quality**

While drinking-water is used for many excipient processes, purified water is also widely used. Because of the well-known potential for microbial growth in deionizers and ultrafiltration or reverse-osmosis systems used to produce purified water, such systems must be properly validated and checked. Proper control methods include the establishment of water quality specifications and corresponding action levels, remedial action when microbial levels are exceeded, and adequate maintenance procedures such as regeneration and sanitation/sterilization.

Appropriate specifications for chemical and microbial quality should be established and periodic testing conducted. Such specifications will vary depending on the process and the point in the process when the water is used. For example, in some cases, if the water is used in later processing steps such as for a final wash of the filter cake, or if the excipient is crystallized from an aqueous system, the water quality standards may need to be higher than normally specified for purified water. This is particularly important where the excipient's intended use is in parenteral dosage forms. The frequency of microbial and chemical testing of purified water depends on a variety of factors, including the test results and the point in the process (e.g. final wash in centrifuge) at which such water is used.

Most purified water and water for injection systems, including reverse-osmosis and ultrafiltration systems, have the potential for endotoxin contamination. If the final excipient is supposed to be pyrogen free or sterile, or will be used in preparing parenteral products, validation of the system to control endotoxins should be conducted and routine testing of the process water for

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<sup>1</sup> Good manufacturing practices for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report*. Geneva, World Health Organization, 1992, Annex 1, Section 17.3 (WHO Technical Report Series, No. 823). In this volume, see p. 104.



## QUALITY ASSURANCE OF PHARMACEUTICALS

endotoxins should be performed (preferably by the LAL (*Limulus* amoebocyte lysate) method).

### **7.2.5 Packaging operations**

When the programme for packaging operations is being set up, particular attention should be given to minimizing the risk of cross-contamination, mix-ups, or substitutions. Different products should not be packaged in close proximity unless there is physical segregation or the use of electronic surveillance.

### **7.2.6 Delivery**

The manufacturer should arrange for the protection of the product after final inspection and testing. Where contractually agreed, this protection should include delivery to destination. Distribution records should be kept.

## 7.3 Good practices in quality control

### **7.3.1 General**

The quality control unit, in addition to having the responsibility and authority to approve or reject all components, in-process materials, packaging materials and finished excipients, and to review production records, etc., should also be responsible for approving or rejecting excipients manufactured, processed, packaged, or held under contract by another company, as well as for approving or rejecting all procedures, specifications and process changes having an effect on the quality of the excipient.

### **7.3.2 Control of starting materials**

All starting materials must be tested or otherwise verified prior to use. Verification should include a certificate of analysis from the supplier and, wherever feasible, an identification test. There should be clear guidance or standard operating procedures established for the approval of each starting material.

Starting materials are usually subjected to an identity test and additional testing to confirm that they meet appropriate specifications. Some starting materials may not be acceptance tested by the manufacturer because of the hazards involved or other valid considerations. In such cases, quality certification for each batch from the vendor should be on file. There should always be some evidence of an attempt by the excipient manufacturer to establish identity, even if it is only a visual examination of containers, examination of labels, or recording of batch numbers from the labels.



### **7.3.3 In-process testing**

In-process inspection and testing should be performed by monitoring the process or by actual sample analysis at defined locations and times. The results should conform to established process parameters or acceptable tolerances. Work instructions should delineate the procedure to follow and how to use the inspection and test data to control the process.

### **7.3.4 Quality records and retention samples**

The manufacturer should establish and maintain procedures for identification, collection, indexing, filing, storage, maintenance and availability of quality records. Quality records should be maintained to demonstrate achievement of the required quality and the effective operation of the quality system. These data should include pertinent subcontractor quality records.

All quality records should be legible and identifiable to the product involved. Quality records should be stored and maintained in such a way that they are readily retrievable, in facilities that provide a suitable environment to minimize deterioration or damage and to prevent loss. Retention times of quality records should be established and recorded. Where agreed contractually, quality records should be made available for evaluation by the purchaser or the purchaser's representative for an agreed period.

All appropriate records relating to inspection and testing must be available for review. Where the process is continuously monitored, acknowledgement must be made of this and the results of the monitoring should be available.

Reserve samples of the released excipient should be retained for one year after the expiry or re-evaluation date, or for one year after distribution is complete. Sample size should be twice the amount required to perform release specification testing.

### **7.3.5 Stability studies**

Many excipient products are very stable and may not require extensive testing to check stability. The stability of some excipients may be affected by undetected changes in starting material specifications, or subtle changes in manufacturing procedures. Excipients may also be shipped in a large variety of different packaging types that can affect their stability (e.g. metal and plastic drums, bags, plastic and glass bottles, bulk tankers).

Some excipients may be similar in chemical structure to other excipients, and some may be mixtures or blends of other excipients. These excipients may be very similar to others within a product group. Minor quantitative differences of some of the components may be the only significant variation from one product to another. For these excipients, a "model product" approach to assess the stability may be appropriate. Stability studies of this type should involve selection of several "model products" that would be expected to simulate the stability of the



product group being assessed. This selection must be scientifically based. Data from stability studies of these “model products” can be used to determine the theoretical stability of similar products.

The full stability testing programme, when needed, usually contains the following features and takes into account historical data:

- The programme should be formalized in writing and ongoing studies should be reviewed at least annually.
- The programme should periodically include a sample from at least one commercial size batch.
- Stability samples should be stored in containers that approximate the primary market container. Simulations of all types of containers are not required, unless there are theoretical reasons to indicate that stability may be affected by container type.
- The samples should be stored under conditions similar to those recommended for the marketed excipient product.
- Additional samples may be stored under stress conditions (e.g. elevated temperature, light, humidity or freezing) if such conditions might reasonably be encountered during distribution and storage.
- Stability-indicating test methods should be used.
- Where stability of the excipient appears to be a significant issue in its use in pharmaceutical manufacturing, additional periodic testing of either the specific material or “model products” may have to be performed to ensure that the expected stability does not significantly change with future batches. The frequency of testing should be determined by the impact that the excipient’s stability may have on its usage.

### **7.3.6 Expiry/re-evaluation dating**

Conducting a stability testing programme does not necessarily mean that expiry dates must be used. Where stability testing indicates a limited shelf-life, the label should declare an expiry date or indicate the need for re-evaluation testing at an appropriate interval to assure quality at time of use.

If the need for special storage conditions exists (e.g. protection from light, heat) such restrictions should be placed on the label.

### **7.3.7 Calibration of measuring and test equipment**

All measuring and test equipment identified as being part of the quality system should be properly calibrated and maintained. This includes all in-process instruments identified as critical quality instruments, as well as test equipment used in the laboratory. The control programme should include the standardization or calibration of reagents, instruments, apparatus, gauges and recording devices at suitable intervals, in accordance with an established written programme containing specific directions, schedules, limits for accuracy and precision, and provi-



## STARTING MATERIALS

sions for remedial action in the event that accuracy and/or precision limits are not met. Reagents, instruments, apparatus, gauges and recording devices not meeting established specifications should not be used. Computer systems used to verify that the product conforms to specifications must be audited to ensure satisfactory performance in the laboratory.



# 3.

## WHO good manufacturing practices: specific pharmaceutical products

### Sterile pharmaceutical products<sup>1</sup>

Introductory note	86
1. General considerations	86
2. Quality control	87
3. Sanitation	87
4. Manufacture of sterile preparations	88
5. Sterilization	93
6. Terminal sterilization	94
7. Aseptic processing and sterilization by filtration	97
8. Personnel	98
9. Premises	100
10. Equipment	101
11. Finishing of sterile products	102
References	102

### Introductory note

This document is a revision of section 17 of Part Three of “Good manufacturing practices [GMP] for pharmaceutical products” (1), which emphasizes specific points for the manufacture of sterile preparations to minimize the risks of microbiological, particulate and pyrogen contamination. It is not exhaustive in character, and some technical requirements may change in line with developments in the field of GMP or advances in engineering design.

### 1. General considerations

1.1 The production of sterile preparations should be carried out in clean areas, entry to which should be through airlocks for personnel and/or for equipment and materials. Clean areas should be maintained to an appropriate standard of cleanliness and supplied with air that has passed through filters of the required efficiency.

1.2 The various operations of component preparation (such as those involving containers and closures), product preparation, filling and sterilization should be

<sup>1</sup> Ref.: WHO Technical Report Series, No 902, 2002, Annex 6, pp. 76–93





carried out in separate areas within a clean area. These areas are classified into four grades (see section 4.1).

1.3 Manufacturing operations are divided here into two categories: first, those where the product is terminally sterilized, and second, those which are conducted aseptically at some or all stages.

## 2. Quality control

2.1 Samples taken for sterility testing should be representative of the whole of the batch, but should, in particular, include samples taken from parts of the batch considered to be most at risk of contamination, for example:

- (a) for products that have been filled aseptically, samples should include containers filled at the beginning and end of the batch and after any significant interruption of work;
- (b) for products that have been heat sterilized in their final containers, consideration should be given to taking samples from that part of the load that is potentially the coolest.

2.2 The sterility of the finished product is ensured by validation of the sterilization cycle in the case of terminally sterilized products, and by “media-fills” runs for aseptically processed products. Batch processing records and, in the case of aseptic processing, environmental quality records, should be examined in conjunction with the results of the sterility tests. The sterility test procedure should be validated for a given product. Pharmacopoeial methods must be used for the validation and performance of the sterility test.

2.3 For injectable products, the water for injection and the intermediate and finished products should be monitored for endotoxins, using an established pharmacopoeial method that has been validated for each type of product. For large-volume infusion solutions, such monitoring of water or intermediates should always be done, in addition to any tests required by an approved monograph for the finished product. When a sample fails a test, the cause of such failure should be investigated and remedial action taken where necessary.

## 3. Sanitation

3.1 The sanitation of clean areas is particularly important. They should be cleaned frequently and thoroughly in accordance with an approved written programme. Monitoring should be regularly undertaken in order to detect the emergence of resistant strains of microorganisms. In view of its limited effectiveness, ultraviolet light should not be used as a substitute for chemical disinfection.

3.2 Disinfectants and detergents should be monitored for microbiological contamination; dilutions should be kept in previously cleaned containers and should

**Table 1. Limits for microbiological contamination<sup>a</sup>**

Grade <sup>b</sup>	Air sample (CFU/m <sup>3</sup> )	Settle plates (diameter 90 mm) (CFU/4 hours) <sup>c</sup>	Contact plates (diameter 55 mm) (CFU/plate)	Glove print (5 fingers) (CFU/glove)
A	<3	<3	<3	<3
B	10	5	5	5
C	100	50	25	—
D	200	100	50	—

<sup>a</sup> These are average values. The grades are defined in section 4.1.

<sup>b</sup> The airborne particulate classification for the four grades is given in Table 2.

<sup>c</sup> Individual settle plates may be exposed for less than 4 hours.

only be stored for defined periods unless sterilized. Disinfectants and detergents used in grade A and B areas (see section 4.1) should be sterilized before use.

3.3 In order to control the microbiological cleanliness of the various grades in operation, the clean areas should be monitored. Where aseptic operations are performed, monitoring should be frequent and methods such as settle plates, and volumetric air and surface sampling (e.g. swabs and contact plates) should be used. The zones should not be contaminated through the sampling methods used in the operations. The results of monitoring should be considered when batch documentation for release of the finished product is reviewed. Both surfaces and personnel should be monitored after critical operations.

3.4 Levels (limits) of detection of microbiological contamination should be established for alert and action purposes, and for monitoring the trends in air quality in the facility. Limits expressed in colony-forming units (CFU) for the microbiological monitoring of clean areas in operation are given in Table 1. The sampling methods and numerical values included in the table are not intended to represent specifications, but are for information only.

## 4. Manufacture of sterile preparations

4.1 Clean areas for the manufacture of sterile products are classified according to the required characteristics of the environment. Each manufacturing operation requires an appropriate environmental cleanliness level in the operational state in order to minimize the risks of particulate or microbiological contamination of the product or materials being handled.

In order to meet “in operation” conditions, these areas should be designed to reach certain specified air-cleanliness levels in the “at rest” occupancy state. This latter state is the condition where the installation is complete, and production equipment has been installed and is operating, but no operating personnel are present. The “in operation” state is the condition where the installation is

**Table 2. Airborne particulate classification for manufacture of sterile pharmaceutical preparations**

Grade	At rest		In operation	
	Maximum number of particles permitted/m <sup>3</sup>		Maximum number of particles permitted/m <sup>3</sup>	
	0.5–5.0µm	>5.0µm	0.5–5.0µm	>5.0µm
A	3500	0	3500	0
B	3500	0	350000	2000
C	350000	2000	3500000	20000
D	3500000	20000	Not defined	Not defined

functioning in the defined operating mode and the specified number of personnel are present.

For the manufacture of sterile pharmaceutical preparations, four grades are distinguished here, as follows:

- *Grade A:* The local zone for high-risk operations, e.g. filling and making aseptic connections. Normally such conditions are provided by a laminar-airflow workstation. Laminar-airflow systems should provide a homogeneous air speed of approximately 0.45 m/s ± 20% (guidance value) at the working position.
- *Grade B:* In aseptic preparation and filling, the background environment for the grade A zone.
- *Grades C and D:* Clean areas for carrying out less critical stages in the manufacture of sterile products.

The airborne particulate classification for the four grades is given in Table 2.

To obtain air of the required characteristics, methods specified by national authorities should be used. It should be noted that:

- In order to reach the B, C and D air grades, the number of air changes should be appropriate for the size of the room and the equipment and personnel present in it. At least 20 air changes per hour are usually required for a room with a good airflow pattern and appropriate high-efficiency particulate air (HEPA) filters.
- Detailed information on methods for determining the microbiological and particulate cleanliness of air, surfaces, etc. is not given here. Reference should be made to other guidelines published in compendia such as the European, Japanese or United States pharmacopoeias, or in documents issued by the European Committee for Standardization and the International Organization for Standardization (ISO).



**Table 3. Comparison of different airborne particulate classification systems for clean areas<sup>a</sup>**

<b>WHO (GMP)</b>	<b>United States (209E)</b>	<b>United States (customary)</b>	<b>ISO/TC (209)</b>	<b>EEC (GMP)</b>
Grade A	M 3.5	Class 100	ISO 5	Grade A
Grade B	M 3.5	Class 100	ISO 5	Grade B
Grade C	M 5.5	Class 10 000	ISO 7	Grade C
Grade D	M 6.5	Class 100 000	ISO 8	Grade D

EEC: European Commission; ISO/TC: International Organization for Standardization Technical Committee.

<sup>a</sup>Source: references 1–4.

The different airborne particulate classification systems for clean areas are shown in Table 3.

4.2 The particulate conditions given in Table 2 for the “at rest” state should be achieved in the absence of the operating personnel after a short “clean-up” period of about 15–20 minutes (guidance value), after completion of the operations. The particulate conditions given in Table 2 for grade A “in operation” should be maintained in the zone immediately surrounding the product whenever the product or open container is exposed to the environment. It is accepted that it may not always be possible to demonstrate conformity with particulate standards at the point of fill when filling is in progress, owing to the generation of particles or droplets from the product itself.

4.3 In order to control the particulate cleanliness of the various clean areas during operation, they should be monitored.

4.4 Appropriate alert and action limits should be set for the results of particulate and microbiological monitoring. If these limits are exceeded, the appropriate corrective actions should be taken, as prescribed in the operating procedures.

4.5 The area grades as specified in sections 4.6–4.14 must be selected by the manufacturer on the basis of the nature of the process operations being performed and validation runs (e.g. sterile media fills). The determination of an appropriate process area environment and a time limit should be based on the microbiological contamination (bioburden) found.

### Terminally sterilized products

4.6 Components and most products should be prepared in at least a grade D environment in order to give low microbial and particulate counts, suitable for filtration and sterilization. Where the product is at unusual risk of microbial contamination (e.g. because it actively supports microbial growth, must be held



for a long period before sterilization, or is necessarily not processed mainly in closed vessels), the preparation should generally be done in a grade C environment.

4.7 The filling of products for terminal sterilization should generally be done in at least a grade C environment.

4.8 Where the product is at unusual risk of contamination from the environment (e.g. because the filling operation is slow or the containers are wide-necked or are necessarily exposed for more than a few seconds before sealing), the filling should be done in a grade A zone with at least a grade C background.

4.9 The preparation and filling of ointments, creams, suspensions and emulsions should generally be done in a grade C environment before terminal sterilization.

### Aseptic preparation

4.10 Components after washing should be handled in at least a grade D environment. The handling of sterile starting materials and components, unless subjected to sterilization or filtration through a microorganism-retaining filter later in the process, should be done in a grade A environment with a grade B background.

4.11 The preparation of solutions which are to be sterile filtered during the process should be done in a grade C environment; if not sterile filtered, the preparation of materials and products should be done in a grade A environment with a grade B background.

4.12 The handling and filling of aseptically prepared products, as well as the handling of exposed sterile equipment, should be done in a grade A environment with a grade B background.

4.13 The transfer of partially closed containers, as used in freeze-drying, should, before stoppering is completed, be done either in a grade A environment with a grade B background or in sealed transfer trays in a grade B environment.

4.14 The preparation and filling of sterile ointments, creams, suspensions and emulsions should be done in a grade A environment with a grade B background when the product is exposed and is subsequently filtered.

### Processing

4.15 Precautions to minimize contamination should be taken during all processing stages, including the stages before sterilization.

4.16 Preparations containing live microorganisms should not be made or containers filled in areas used for the processing of other pharmaceutical products; however, vaccines consisting of dead organisms or of bacterial extracts may be dispensed into containers, after validated inactivation and validated



cleaning procedures, in the same premises as other sterile pharmaceutical products.

4.17 The validation of aseptic processing should include simulating the process using a nutrient medium. The form of the nutrient medium used should generally be equivalent to the dosage form of the product. The process-simulation test should imitate as closely as possible the routine aseptic manufacturing process and include all the critical subsequent manufacturing steps. Consideration should be given to simulation of the worst expected condition. The process-simulation test should be repeated at defined intervals and after any significant modification to the equipment and process. The number of containers used for a medium fill should be sufficient to ensure a valid evaluation. For small batches, the number of containers for the medium fill should be at least equal to the size of the product batch.

4.18 Care should be taken to ensure that any validation does not compromise the processes.

4.19 Water sources, water-treatment equipment and treated water should be monitored regularly for chemicals, biological contamination and contamination with endotoxins to ensure that the water complies with the specifications appropriate to its use. Records should be maintained of the results of the monitoring and of any action taken.

4.20 Activities in clean areas, especially when aseptic operations are in progress, should be kept to a minimum, and the movement of personnel should be controlled and methodical, so as to avoid excessive shedding of particles and organisms due to over-vigorous activity. The ambient temperature and humidity should not be uncomfortably high because of the nature of the garments worn.

4.21 The presence of containers and materials liable to generate fibres should be minimized in clean areas and avoided completely when aseptic work is in progress.

4.22 Components, bulk-product containers and equipment should be handled after the final cleaning process in such a way that they are not recontaminated. The stage of processing of components, bulk-product containers and equipment should be properly identified.

4.23 The interval between the washing and drying and the sterilization of components, bulk-product containers and equipment, as well as between sterilization and use, should be as short as possible and subject to a time-limit appropriate to the validated storage conditions.

4.24 The time between the start of the preparation of a solution and its sterilization or filtration through a bacteria-retaining filter should be as short as possible. A maximum permissible time should be set for each product that takes into account its composition and the prescribed method of storage.



4.25 Any gas that is used to purge a solution or blanket a product should be passed through a sterilizing filter.

4.26 The bioburden of products should be monitored before sterilization. There should be a working limit on the contamination of products immediately before sterilization that is related to the efficiency of the method to be used and the risk of pyrogens. All solutions, in particular large-volume parenterals, should be passed through a microorganism-retaining filter, if possible immediately before the filling process. Where aqueous solutions are held in sealed vessels, any pressure-release outlets should be protected, e.g. by hydrophobic microbiological air filters.

4.27 Components, bulk-product containers, equipment and any other articles required in a clean area where aseptic work is in progress should be sterilized and, wherever possible, passed into the area through double-ended sterilizers sealed into the wall. Other procedures that prevent the introduction of contamination (e.g. triple wrapping) may be acceptable in some circumstances.

4.28 The efficacy of any new processing procedure should be validated, and the validation should be repeated at regular intervals thereafter or when any significant change is made in the process or equipment.

## 5. Sterilization

5.1 Whenever possible, products intended to be sterile should preferably be terminally sterilized by heat in their final container. Where it is not possible to carry out terminal sterilization by heating due to the instability of a formulation, a decision should be taken to use an alternative method of terminal sterilization following filtration and/or aseptic processing.

5.2 Sterilization can be achieved by the use of moist or dry heat, by irradiation with ionizing radiation (but not with ultraviolet radiation unless the process is thoroughly validated), by ethylene oxide (or other suitable gaseous sterilizing agents) or by filtration with subsequent aseptic filling of sterile final containers. Each method has its particular advantages and disadvantages. Where possible and practicable, heat sterilization is the method of choice.

5.3 The microbiological contamination of starting materials should be minimal, and their bioburden should be monitored before sterilization. Specifications should include requirements for microbiological quality when the need for this has been indicated by monitoring.

5.4 All sterilization processes must be validated. Particular attention should be given when the adopted sterilization method is not in accordance with pharmacopoeial or other national standards or when it is used for a preparation that is not a simple aqueous or oily solution.



## QUALITY ASSURANCE OF PHARMACEUTICALS

5.5 Before any sterilization process is adopted, its suitability for the product and its efficacy in achieving the desired sterilizing conditions in all parts of each type of load to be processed should be demonstrated by physical measurements and by biological indicators, where appropriate. The validity of the process should be verified at scheduled intervals, at least annually, and whenever significant modifications have been made to the equipment. Records should be kept of the results.

5.6 For effective sterilization, the whole of the material should be subjected to the required treatment and the process should be designed to ensure that this is achieved.

5.7 Biological indicators should be considered only as an additional method of monitoring the sterilization process. They should be stored and used according to the manufacturer's instructions, and their quality checked by positive controls. If they are used, strict precautions should be taken to avoid any transfer of microbiological contamination from them.

5.8 There should be a clear means of differentiating products that have not been sterilized from those that have. Each basket, tray, or other carrier of products or components should be clearly labelled with the name of the material, its batch number, and an indication of whether or not it has been sterilized. Indicators such as autoclave tape may be used, where appropriate, to indicate whether or not a batch (or sub-batch) has passed through a sterilization process, but they do not give a reliable indication that the batch is, in fact, sterile.

5.9 Sterilization records should be available for each sterilization run. They should be approved as part of the batch-release procedure.

## 6. Terminal sterilization

### Sterilization by heat

6.1 Each heat-sterilization cycle should be recorded by means of appropriate equipment of suitable accuracy and precision, e.g. on a time/temperature chart with a suitably large scale. The temperature should be recorded by a probe at the coolest part of the load or loaded chamber, this point having been determined during the validation; the temperature should preferably be checked against a second independent temperature probe located at the same position. The chart, or a photocopy of it, should form part of the batch record. Chemical or biological indicators may also be used but should not take the place of physical controls.

6.2 Sufficient time must be allowed for the whole of the load to reach the required temperature before measurement of the sterilizing time is started. This time must be determined for each type of load to be processed.





6.3 After the high-temperature phase of a heat sterilization cycle, precautions should be taken against contamination of a sterilized load during cooling. Any cooling fluid or gas in contact with the product should be sterilized.

#### Sterilization by moist heat

6.4 Sterilization by moist heat (heating in an autoclave) is suitable only for water-wettable materials and aqueous formulations. Both temperature and pressure should be used to monitor the process. The temperature recorder should normally be independent of the controller, and there should be an independent temperature indicator, the reading from which should be routinely checked against the chart recorder during the sterilization period. For sterilizers fitted with a drain at the bottom of the chamber, it may also be necessary to record the temperature at this position throughout the sterilization period. There should be regular leak tests on the chamber when a vacuum phase is part of the cycle.

6.5 The items to be sterilized, other than products in sealed containers, should be wrapped in a material that allows the removal of air and the penetration of steam but prevents recontamination after sterilization. All parts of the load should be in contact with water or saturated steam at the required temperature for the required time.

6.6 Care should be taken to ensure that the steam used for sterilization is of suitable quality and does not contain additives at a level that could cause contamination of the product or equipment.

#### Sterilization by dry heat

6.7 Sterilization by dry heat may be suitable for non-aqueous liquids or dry powder products. The process used should include air circulation within the chamber and the maintenance of a positive pressure to prevent the entry of non-sterile air. If air is supplied, it should be passed through a microorganism-retaining filter (e.g. an HEPA filter). Where sterilization by dry heat is also intended to remove pyrogens, challenge tests using endotoxins will be required as part of the validation.

#### Sterilization by radiation

6.8 Sterilization by radiation is used mainly for the sterilization of heat-sensitive materials and products. Many pharmaceutical products and some packaging materials are radiation-sensitive, so this method is permissible only when the absence of deleterious effects on the product has been confirmed experimentally. Ultraviolet irradiation is not an acceptable method for terminal sterilization.



## QUALITY ASSURANCE OF PHARMACEUTICALS

6.9 If sterilization by radiation is carried out by an outside contractor, the manufacturer is responsible for ensuring that the requirements of section 6.8 are met, and that the sterilization process is validated. The responsibilities of the radiation plant operator (e.g. for using the correct dose) should also be specified.

6.10 During the sterilization procedure, the radiation dose should be measured. For this purpose, the dosimeters used must be independent of the dose rate and must provide a quantitative measurement of the dose received by the product itself. Dosimeters should be inserted in the load in sufficient number, and close enough together to ensure that there is always a dosimeter in the chamber. Where plastic dosimeters are employed, they should be used within the time-limit of their calibration. Dosimeter absorbances should be read shortly after exposure to radiation. Biological indicators may be used only as an additional control. Radiation-sensitive colour discs may be used to differentiate between packages that have been subjected to irradiation and those that have not; they are not indicators of successful sterilization. The information obtained should constitute part of the batch record.

6.11 Validation procedures should ensure that consideration is given to the effects of variations in the density of the packages.

6.12 Handling procedures should prevent any misidentification of irradiated and non-irradiated materials. Each package should carry a radiation-sensitive indicator to show whether or not it has been subjected to radiation treatment.

6.13 The total radiation dose should be administered within a predetermined period of time.

### Sterilization by gases and fumigants

6.14 This method of sterilization should only be used for products where there is no suitable alternative.

6.15 Various gases and fumigants may be used for sterilization (e.g. ethylene oxide, hydrogen peroxide vapour). Ethylene oxide should be used only when no other method is practicable. During process validation it should be shown that the gas has no damaging effect on the product and that the conditions and time allowed for degassing are such as to reduce any residual gas and reaction products to defined acceptable limits for the type of product or material concerned. These limits should be incorporated in the specifications.

6.16 Direct contact between gas and microorganisms is essential; precautions should therefore be taken to avoid the presence of organisms likely to be enclosed in materials such as crystals or dried protein. The nature and quantity of packaging materials can significantly affect the process.



6.17 Before exposure to the gas, materials should be brought into equilibrium with the humidity and temperature required by the process. This requirement should be balanced against the need to minimize the waiting time before sterilization.

6.18 Each sterilization cycle should be monitored with suitable biological indicators, using the appropriate number of test pieces distributed throughout the load. The information so obtained should form part of the batch record.

6.19 Biological indicators should be stored and used according to the manufacturer's instructions, and their performance checked by positive controls.

6.20 For each sterilization cycle, records should be made of the time taken to complete the cycle, of the pressure, temperature and humidity within the chamber during the process, and of the gas concentration. The pressure and temperature should be recorded on a chart throughout the cycle. The records should form part of the batch record.

6.21 After sterilization, the load should be stored in a controlled manner under ventilated conditions to allow concentrations of residual gas and reaction products to fall to their prescribed levels. This process should be validated.

## 7. Aseptic processing and sterilization by filtration

7.1 The objective of aseptic processing is to maintain the sterility of a product that is assembled from components, each of which has been sterilized by one of the above methods (see sections 5 and 6).

7.2 The operating conditions should be such as to prevent microbial contamination.

7.3 In order to maintain the sterility of the components and the product during aseptic processing, careful attention needs to be given to: (a) the environment; (b) the personnel; (c) the critical surfaces; (d) the container/closure sterilization and transfer procedures; (e) the maximum holding period of the product before filling into the final container; and (f) the sterilizing filter.

7.4 Certain solutions and liquids that cannot be sterilized in the final container can be filtered through a sterile filter of nominal pore size  $0.22\mu\text{m}$  (or less), or with at least equivalent microorganism-retaining properties, into a previously sterilized container. Such filters can remove bacteria and moulds, but not all viruses or mycoplasmas. Consideration should be given to complementing the filtration process with some degree of heat treatment.

7.5 Owing to the potential additional risks of the filtration method as compared with other sterilization processes, a double filter layer or second filtration via a further sterilized microorganism-retaining filter immediately prior to filling may



## QUALITY ASSURANCE OF PHARMACEUTICALS

be advisable. The final sterile filtration should be carried out as close as possible to the filling point.

7.6 The fibre-shedding characteristics of filters should be minimal (virtually zero). Asbestos-containing filters must not be used under any circumstances.

7.7 The integrity of the filter should be checked by an appropriate method such as a bubble-point, diffusive-flow or pressure-hold test, immediately after use (it may also be useful to test the filter in this way before use). The time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter should be determined during validation, and any significant differences from these values should be noted and investigated. The results of these checks should be recorded in the batch record. The integrity of critical gas and air vent filters should be confirmed after use. The integrity of other filters should be confirmed at appropriate intervals. Consideration should be given to increased monitoring of filter integrity in processes that involve harsh conditions, e.g. the circulation of high-temperature air.

7.8 The same filter should not be used for more than 1 working day unless such use has been validated.

7.9 The filter should not affect the product either by removing ingredients from it or by releasing substances into it.

## 8. Personnel

8.1 Only the minimum number of personnel required should be present in clean areas; this is particularly important during aseptic processes. Inspections and controls should be conducted from outside such areas as far as possible.

8.2 All personnel (including those concerned with cleaning and maintenance) employed in such areas should receive initial and regular training in disciplines relevant to the correct manufacture of sterile products, including hygiene and the basic elements of microbiology. When outside staff who have not received such training (e.g. building or maintenance contractors) need to be brought in, particular care should be taken over their instruction and supervision.

8.3 Staff who have been engaged in the processing of animal-tissue materials or of cultures of microorganisms other than those used in the current manufacturing process should not enter sterile-product areas unless rigorous and clearly defined decontamination procedures have been followed.

8.4 High standards of personal hygiene and cleanliness are essential, and personnel involved in the manufacture of sterile preparations should be instructed to report any conditions that may cause the shedding of abnormal numbers or types of contaminants; periodic health checks for such conditions are desirable. The action to be taken in respect of personnel who might be introduc-



ing undue microbiological hazards should be decided by a designated competent person.

8.5 Outdoor clothing should not be brought into clean areas, and personnel entering changing rooms should already be clad in standard factory protective garments. Changing and washing should follow a written procedure designed to minimize the contamination of clean area clothing or the carry-through of contaminants to clean areas.

8.6 Wrist-watches and jewellery should not be worn in clean areas, and cosmetics that can shed particles should not be used.

8.7 The clothing worn and its quality should be appropriate for the process and the grade of the working area (workplace). It should be worn in such a way as to protect the product from contamination. The clothing required for each grade is as follows:

- *Grade D.* The hair and, where relevant, beard and moustache should be covered. Protective clothing and appropriate shoes or overshoes should be worn. Appropriate measures should be taken to avoid any contamination from outside the clean area.
- *Grade C.* The hair and, where relevant, beard and moustache should be covered. A single or two-piece trouser suit, gathered at the wrists and with a high neck, and appropriate shoes or overshoes should be worn. The clothing should shed virtually no fibres or particulate matter.
- *Grades A/B.* Headgear should totally enclose the hair and, where relevant, beard and moustache. A single or two-piece trouser suit, gathered at the wrists and with a high neck, should be worn. The headgear should be tucked into the neck of the suit. A face mask should be worn to prevent the shedding of droplets. Appropriate, sterilized, non-powdered rubber or plastic gloves and sterilized or disinfected footwear should be worn. Trouser-bottoms should be tucked inside the footwear and garment sleeves into the gloves. The protective clothing should shed virtually no fibres or particulate matter and should retain particles shed by the body.

8.8 Outdoor clothing should not be brought into changing rooms leading to grade B and C rooms. For every worker in a grade A/B room, clean sterilized or adequately sanitized protective garments should be provided at each work session, or at least once a day if monitoring results justify this. Gloves should be regularly disinfected during operations. Masks and gloves should be changed at least at every working session. The use of disposable clothing may be necessary.

8.9 Clothing used in clean areas should be laundered or cleaned in such a way that it does not gather additional particulate contaminants that can later be shed. Separate laundry facilities for such clothing are desirable. If fibres are damaged by inappropriate cleaning or sterilization, there may be an increased risk of shedding



particles. Washing and sterilization operations should follow standard operating procedures.

## 9. Premises

9.1 All premises should, as far as possible, be designed to avoid the unnecessary entry of supervisory or control personnel. Grade B areas should be designed so that all operations can be observed from outside.

9.2 In clean areas, all exposed surfaces should be smooth, impervious and unbroken in order to minimize the shedding or accumulation of particles or microorganisms and to permit the repeated application of cleaning agents and disinfectants, where used.

9.3 To reduce the accumulation of dust and to facilitate cleaning, there should be no uncleanable recesses and a minimum of projecting ledges, shelves, cupboards and equipment. Doors should be carefully designed to avoid uncleanable recesses; sliding doors are undesirable for this reason.

9.4 False ceilings should be sealed to prevent contamination from the space above them.

9.5 Pipes and ducts and other utilities should be installed so that they do not create recesses, unsealed openings and surfaces that are difficult to clean.

9.6 Sinks and drains should be avoided wherever possible and should be excluded from grade A/B areas where aseptic operations are carried out. Where installed, they should be designed, located and maintained so as to minimize the risks of microbiological contamination; they should be fitted with effective, easily cleanable traps and with air breaks to prevent back-flow. Any floor channels should be open and easily cleanable and be connected to drains outside the area in a manner that prevents the ingress of microbiological contaminants.

9.7 Changing rooms should be designed as airlocks and used to separate the different stages of changing, thus minimizing particulate and microbiological contamination of protective clothing. They should be effectively flushed with filtered air. The use of separate changing rooms for entering and leaving clean areas is sometimes necessary. Hand-washing facilities should be provided only in the changing rooms, not in areas where aseptic work is done.

9.8 Airlock doors should not be opened simultaneously. An interlocking system and a visual and/or audible warning system can be installed to prevent the opening of more than one door at a time.

9.9 A filtered air supply should be used to maintain a positive pressure and an airflow relative to surrounding areas of a lower grade under all operational conditions; it should flush the area effectively. Adjacent rooms of different grades should have a pressure differential of approximately 10–15 pascals (guidance



value). Particular attention should be paid to the protection of the zone of greatest risk, i.e. the immediate environment to which the product and the cleaned components in contact with it are exposed. The various recommendations regarding air supplies and pressure differentials may need to be modified where it becomes necessary to contain certain materials, e.g. pathogenic, highly toxic, radioactive or live viral or bacterial materials or products. The decontamination of the facilities and the treatment of air leaving a clean area may be necessary for some operations.

9.10 It should be demonstrated that airflow patterns do not present a contamination risk; for example, care should be taken to ensure that particles from a particle-generating person, operation or machine are not conveyed to a zone of higher product risk.

9.11 A warning system should be included to indicate failure in the air supply. An indicator of pressure difference should be fitted between areas where this difference is important, and the pressure difference should be regularly recorded.

9.12 Consideration should be given to restricting unnecessary access to critical filling areas, e.g. grade A filling zones, by means of a physical barrier.

## 10. Equipment

10.1 A conveyor belt should not pass through a partition between a grade A or B clean area and a processing area of lower air cleanliness, unless the belt itself is continuously sterilized (e.g. in a sterilizing tunnel).

10.2 Whenever possible, equipment used for processing sterile products should be chosen so that it can be effectively sterilized by steam or dry heat or other methods.

10.3 As far as possible, equipment fittings and services should be designed and installed so that operations, maintenance and repairs can be carried out outside the clean area. Equipment that has to be taken apart for maintenance should be resterilized after complete reassembly, wherever possible.

10.4 When equipment maintenance is carried out within a clean area, clean instruments and tools should be used, and the area should be cleaned and disinfected again, where appropriate, before processing recommences if the required standards of cleanliness and/or asepsis have not been maintained during the maintenance work.

10.5 All equipment, including sterilizers, air-filtration systems, and water-treatment systems, including stills, should be subject to planned maintenance, validation and monitoring; its approved use following maintenance work should be documented.



10.6 Water-treatment plants and distribution systems should be designed, constructed and maintained so as to ensure a reliable source of water of an appropriate quality. They should not be operated beyond their designed capacity. Consideration should be given to including a testing programme in the maintenance of a water system. Water for injection should be produced, stored and distributed in a manner which prevents the growth of microorganisms, e.g. by constant circulation at a temperature above 70°C or not more than 4°C.

## 11. Finishing of sterile products

11.1 Containers should be closed by appropriately validated methods. Samples should be checked for integrity according to appropriate procedures.

11.2 Containers sealed under vacuum should be sampled and the samples tested, after an appropriate predetermined period, to ensure that the vacuum has been maintained.

11.3 Filled containers of parenteral products should be inspected individually. When inspection is done visually, it should be done under suitable and controlled conditions of illumination and background. Operators doing the inspection should pass regular eyesight checks, with spectacles if worn, and be allowed frequent breaks from inspection. Where other methods of inspection are used, the process should be validated and the performance of the equipment checked at intervals. The results should be recorded.

## References

1. Good manufacturing practices for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report*. Geneva, World Health Organization, 1992, Annex 1 (WHO Technical Report Series, No. 823).
2. *Airborne particulate cleanliness classes in cleanrooms and clean zones. Federal Standard 209E*. Mount Prospect, IL, Institute of Environmental Sciences, 1992.
3. *Cleanrooms and associated controlled environments. Part 1: classification of airborne particulates*. Geneva, International Organization for Standardization, 1999.
4. *The rules governing medicinal products in the European Union. Vol. 4. Good manufacturing practices: medicinal products for human and veterinary use*. Brussels, European Commission, 1998.





## Biological products<sup>1</sup>

1. Scope of these guidelines	103
2. Principles	103
3. Personnel	104
4. Premises and equipment	105
5. Animal quarters and care	108
6. Production	108
7. Labelling	109
8. Lot processing records (protocols) and distribution records	110
9. Quality assurance and quality control	111
Authors	112
Acknowledgements	112
References	113

### 1. Scope of these guidelines

These guidelines are intended to complement those provided in “Good manufacturing practices for pharmaceutical products” (1).

The regulatory procedures necessary to control biological products are in large part determined by the sources of products and methods of manufacture. Manufacturing procedures within the scope of these guidelines include:

- growth of strains of microorganisms and eukaryotic cells,
- extraction of substances from biological tissues, including human, animal and plant tissues (allergens),
- recombinant DNA (rDNA) techniques,
- hybridoma techniques,
- propagation of microorganisms in embryos or animals.

Biological products manufactured by these methods include allergens, antigens, vaccines, hormones, cytokines, enzymes, human whole blood and plasma derivatives, immune sera, immunoglobulins (including monoclonal antibodies), products of fermentation (including products derived from rDNA) and diagnostic agents for *in vitro* use.

### 2. Principles

The manufacture of biological products shall be undertaken in accordance with the basic principles of good manufacturing practices (GMP). The points covered

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<sup>1</sup> Good manufacturing practices for biological products. In: *WHO Expert Committee on Biological Standardization. Forty-second report*. Geneva, World Health Organization, 1992, Annex 1 (WHO Technical Report Series, No. 822) and *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report*. Geneva, World Health Organization, 1993, Annex 3 (WHO Technical Report Series, No. 834).



by these guidelines should therefore be considered supplementary to the general requirements set out in “Good manufacturing practices for pharmaceutical products” (1), and relate specifically to the production and control of biological products. In drawing up these guidelines, due consideration was given to the draft “Guidelines for national authorities on quality assurance for biological products”, the final version of which appears as Annex 2 to the forty-second report of the WHO Expert Committee on Biological Standardization (2).

The way in which biological products are produced, controlled and administered makes some particular precautions necessary. Unlike conventional pharmaceutical products, which are normally produced and controlled using reproducible chemical and physical techniques, biological products are manufactured by methods involving biological processes and materials, such as cultivation of cells or extraction of material from living organisms. These processes display inherent variability, so that the range and nature of by-products are variable. For this reason, in the manufacture of biological products full adherence to GMP is necessary for all production steps, beginning with those from which the active ingredients are produced.

Control of biological products nearly always involves biological techniques that have a greater variability than physicochemical determinations. In-process controls take on a great importance in the manufacture of biological products because certain deficiencies may not be revealed by testing the finished product.

The present guidelines do not lay down detailed requirements for specific classes of biological products, and attention is therefore directed to other guidance issued by WHO, and in particular to the Requirements for Biological Substances, which include requirements for vaccines (2, Annex 7).

### 3. Personnel

3.1 The manufacturing establishment and its personnel shall be under the authority of a person who has been trained in the techniques used in manufacturing biological substances and who possesses the scientific knowledge upon which the manufacture of these products is based. The personnel shall include specialists with training appropriate to the products made in the establishment.

3.2 Personnel required to work in clean and aseptic areas should be selected with care, to ensure that they may be relied upon to observe the appropriate codes of practice and are not subject to any disease or condition that could compromise the integrity of the product microbiologically or otherwise. High standards of personal hygiene and cleanliness are essential. Staff should be instructed to report any conditions (e.g. diarrhoea, coughs, colds, infected skin or hair, wounds, fever of unknown origin) that may cause the shedding of abnormal numbers or types of organisms into the working environment. Health checks on personnel for such conditions should be required before employment and periodically thereafter. Any changes in health status that could adversely affect the





quality of the product shall preclude the person concerned from working in the production area.

3.3 Only the minimum number of personnel required should be present in clean and aseptic areas when work is in progress. Inspection and control procedures should be conducted from outside these areas as far as possible.

3.4 During the working day, personnel shall not pass from areas where live microorganisms or animals are handled to premises where other products or organisms are handled unless clearly defined decontamination measures, including a change of clothing and shoes, are followed. Persons not concerned with the production process should not enter the production area except for essential purposes, and in that case they shall be supplied with sterile protective clothing.

3.5 The staff engaged in the manufacturing process should be separate from the staff responsible for animal care.

3.6 The names and qualifications of those responsible for approving lot processing records (protocols) should be registered with the national control authority.

3.7 To ensure the manufacture of high-quality products, personnel should be trained in good manufacturing and laboratory practices in appropriate fields such as bacteriology, virology, biometry, chemistry, medicine, immunology and veterinary medicine.

3.8 Training records should be maintained and periodic assessments of the effectiveness of training programmes should be made.

3.9 All personnel engaged in production, maintenance, testing and animal care (and inspectors) should be vaccinated with appropriate vaccines and, where appropriate, be submitted to regular testing for evidence of active tuberculosis. Apart from the obvious problem of exposure of staff to infectious agents, potent toxins or allergens, it is necessary to avoid the risk of contamination of a production batch with these agents.

3.10 Where BCG vaccines are being manufactured, access to production areas shall be restricted to staff who are carefully monitored by regular health checks. In the case of manufacture of products derived from human blood or plasma, vaccination of workers against hepatitis B is recommended.

## 4. Premises and equipment

4.1 As a general principle, buildings must be located, designed, constructed, adapted and maintained to suit the operations to be carried out within them. Laboratories, operating rooms and all other rooms and buildings (including those for animals) that are used for the manufacture of biological products shall be designed and constructed of materials of the highest standard so that cleanliness, especially freedom from dust, insects and vermin, can be maintained.



## QUALITY ASSURANCE OF PHARMACEUTICALS

4.2 Interior surfaces (walls, floors and ceilings) shall be smooth and free from cracks; they shall not shed matter and shall permit easy cleaning and disinfection. Drains should be avoided wherever possible and, unless essential, should be excluded from aseptic areas. Where installed they should be fitted with effective, easily cleanable traps and with breaks to prevent back-flow. The traps may contain electrically operated heating devices or other means for disinfection. Any floor channels should be open, shallow and easily cleanable and be connected to drains outside the area in a manner that prevents ingress of microbial contaminants.

4.3 Sinks shall be excluded from aseptic areas. Any sink installed in other clean areas shall be of suitable material such as stainless steel, without an overflow, and be supplied with water of potable quality. Adequate precautions shall be taken to avoid contamination of the drainage system with dangerous effluents. Airborne dissemination of pathogenic microorganisms and viruses used for production and the possibility of contamination by other types of viruses or substances during the production process, including those from personnel, shall be avoided.

4.4 Lighting, heating, ventilation and, if necessary, air-conditioning should be designed to maintain a satisfactory temperature and relative humidity, to minimize contamination and to take account of the comfort of personnel working in protective clothing. Buildings shall be in a good state of repair. The condition of the buildings should be reviewed regularly and repairs carried out when and where necessary. Special care should be exercised to ensure that building repair or maintenance operations do not compromise products. Premises should provide sufficient space to suit the operations to be carried out, allowing an efficient flow of work and effective communication and supervision. All buildings and rooms shall be clean and sanitary at all times. If rooms intended for the manufacture of biological substances are used for other purposes, they shall be cleaned thoroughly and, if necessary, sanitized before the manufacture of biological substances is resumed. Areas used for processing animal tissue materials and microorganisms not required for the current manufacturing process and for performing tests involving animals or microorganisms must be separated from premises used for manufacturing sterile biological products and have completely separate ventilation systems and separate staff.

4.5 If certain products are to be produced on a campaign basis, the layout and design of the premises and equipment shall permit effective decontamination by fumigation, where necessary, as well as cleaning and sanitizing after the production campaign.

4.6 Seed lots and cell banks used for the production of biological products should be stored separately from other material. Access should be restricted to authorized personnel.

4.7 Live organisms shall be handled in equipment that ensures that cultures are maintained in a pure state and are not contaminated during processing.



## SPECIFIC PHARMACEUTICAL PRODUCTS

4.8 Products such as killed vaccines, including those made by rDNA techniques, toxoids and bacterial extracts may after inactivation be dispensed into containers on the same premises as other sterile biological products, providing that adequate decontamination measures are taken after filling, including, if appropriate, sterilization and washing.

4.9 Spore-forming organisms shall be handled in facilities dedicated to this group of products until the inactivation process is accomplished. For *Bacillus anthracis*, *Clostridium botulinum* and *Clostridium tetani*, strictly dedicated facilities should be utilized for each individual product. Where campaign manufacture of spore-forming organisms occurs in a facility or suite of facilities, only one product should be processed at any one time.

4.10 Dedicated facilities and equipment shall be used for the manufacture of medicinal products derived from human blood or plasma.

4.11 All containers of biological substances, regardless of the stage of manufacture, shall be identified by securely attached labels. Cross-contamination should be prevented by adoption of some or all of the following measures:

- processing and filling in segregated areas;
- avoiding manufacture of different products at the same time, unless they are effectively segregated;
- containing material transfer by means of airlocks, air extraction, clothing change and careful washing and decontamination of equipment;
- protecting against the risks of contamination caused by recirculation of untreated air, or by accidental re-entry of extracted air;
- using “closed systems” of manufacture;
- taking care to prevent aerosol formation (especially by centrifugation and blending);
- excluding pathological specimens sent in for diagnosis from areas used for manufacturing biological substances;
- using containers that are sterilized or are of documented low “bioburden”.

4.12 Positive-pressure areas should be used to process sterile products, but negative pressure is acceptable in specific areas where pathogens are processed. In general, any organisms considered to be pathogenic should be handled within specifically designed areas under negative pressures, in accordance with containment requirements for the product concerned.

4.13 Air-handling units should be dedicated to the processing area concerned. Air from operations involving pathogens shall not be recirculated and, in the cases of organisms in a group above Risk Group 2 (3), shall be exhausted through sterilizing filters that are regularly checked for performance.

4.14 Specific decontamination systems should be considered for effluent when infectious and potentially infectious materials are used for production.



## QUALITY ASSURANCE OF PHARMACEUTICALS

4.15 Pipework, valves and vent filters shall be properly designed to facilitate cleaning and sterilization. Valves on fermentation vessels shall be completely steam-sterilizable. Air-vent filters shall be hydrophobic and shall be validated for their designated use.

4.16 Small stocks of substances that have to be measured or weighed during the production process (e.g. buffers) may be kept in the production area, provided that they are not returned to the general stocks. Otherwise, dry materials used to formulate buffers, culture media, etc. should be weighed and put into solution in a contained area outside the purification and aseptic areas in order to minimize particulate contamination of the product.

### **5. Animal quarters and care<sup>1</sup>**

5.1 Animals are used for the manufacture and control of a number of biological products. Animals shall be accommodated in separate buildings with self-contained ventilation systems. The buildings' design and construction materials shall permit maintenance in a clean and sanitary condition free from insects and vermin. Facilities for animal care shall include isolation units for quarantine of incoming animals and provision for vermin-free food storage. Provision shall also be made for animal inoculation rooms, which shall be separate from the postmortem rooms. There shall be facilities for the disinfection of cages, if possible by steam, and an incinerator for disposing of waste and of dead animals.

5.2 The health status of animals from which starting materials are derived and of those used for quality control and safety testing should be monitored and recorded. Staff employed in animal quarters must be provided with special clothing, changing facilities and showers. Where monkeys are used for the production or quality control of biological products, special consideration is required, as laid down in the revised Requirements for Biological Substances No. 7 (Requirements for Poliomyelitis Vaccine (Oral)) (5).

### **6. Production**

6.1 Standard operating procedures shall be available and maintained up to date for all manufacturing operations.

6.2 Specifications for starting materials should include details of their source, origin and method of manufacture and of the controls applied, in particular microbiological controls, to ensure their suitability for use. Release of a finished product is conditional on satisfactory results being obtained in the tests on starting materials.

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<sup>1</sup> General requirements for animal quarters, care and quarantine are given in reference 4.



6.3 Media and cultures shall be added to fermenters and other vessels under carefully controlled conditions to avoid contamination. Care shall be taken to ensure that vessels are correctly connected when cultures are added.

6.4 If possible, media should be sterilized *in situ*. In-line sterilizing filters for routine addition of gases, media, acids, alkalis, defoaming agents, etc. to fermenters should be used where possible.

6.5 Careful consideration should be given to the validation of sterilization methods.

6.6 When an inactivation process is performed during manufacture, measures should be taken to avoid the risk of cross-contamination between treated and untreated products.

6.7 A wide variety of equipment is used for chromatography; in general such equipment should be dedicated to the purification of one product and should be sterilized or sanitized between batches. Problems of decontamination and purification may arise through repeated use of the same equipment at the same or different stages of processing. The life span of columns and the sterilization method shall be defined. Particular care should be given to monitoring microbial loads and endotoxins.

## 7. Labelling

7.1 All products shall be clearly identified by labels. The labels used must remain permanently attached to the containers under all storage conditions and an area of the container should be left uncovered to allow inspection of the contents. If the final container is not suitable for labelling (for example a capillary tube), it should be in a labelled package.

7.2 The information given on the label on the container and the label on the package shall be approved by the national control authority.

7.3 The label on the container shall show:

- the name of the drug product;
- a list of the active ingredients and the amount of each present, with a statement of the net contents, e.g. number of dosage units, weight or volume;
- the batch or final lot number assigned by the manufacturer;
- the expiry date;
- recommended storage conditions or handling precautions that may be necessary;
- directions for use, and warnings and precautions that may be necessary;
- the nature and amount of any substance used in the preparation of the biological product that is likely to give rise to an adverse reaction in some recipients;



## QUALITY ASSURANCE OF PHARMACEUTICALS

— the name and address of the manufacturer or the company and/or the person responsible for placing the drug on the market.

7.4 The label on the package shall, in addition to the information shown on the label on the container, show at least the nature and amount of any preservative or additive in the product.

7.5 The leaflet in the package should provide instructions for the use of the product, and mention any contraindications or potential adverse reactions.

### **8. Lot processing records (protocols) and distribution records**

8.1 Processing records of regular production lots must provide a complete account of the manufacturing history of each lot of a biological preparation, showing that it has been manufactured, tested, dispensed into containers and distributed in accordance with the licensed procedures.

8.2 A separate processing record should be prepared for each lot of biological product, and should include the following information:

- the name and dosage of the product;
- the date of manufacture;
- the lot identification number;
- the complete formulation of the lot, including identification of seed or starting materials;
- the batch number of each component used in the formulation;
- the yield obtained at different stages of manufacture of the lot;
- a duly signed record of each step followed, precautions taken and special observations made throughout the manufacture of the lot;
- a record of all in-process control tests and of the results obtained;
- a specimen of the label;
- identification of packaging materials, containers and closures used;
- a dated signature of the expert responsible for approving the manufacturing operations;
- an analytical report, dated and signed by the responsible expert, showing whether the lot complies with the specifications described in the standard operating procedure registered with the national control authority;
- a record of the decision regarding the release or rejection of the lot by the quality control department and, if the lot is rejected, a record of its disposal or utilization.

8.3 The records shall be of a type approved by the national control authority. They shall be retained for at least two years after the expiry date of a lot or batch of a biological product and be available at all times for inspection by the national control authority.





8.4 Records must make it possible to trace all steps in the manufacture and testing of a lot, and should include records of sterilization of all apparatus and materials used in its manufacture. Distribution records must be kept in a manner that permits rapid recall of any particular lot, if necessary.

## 9. Quality assurance and quality control

9.1 The quality assurance and/or quality control department should have the following principal duties:

- to prepare detailed instructions for each test and analysis;
- to ensure adequate identification and segregation of test samples to avoid mix-up and cross-contamination;
- to ensure that environmental monitoring and equipment validation are conducted as appropriate for evaluating the adequacy of the manufacturing conditions;
- to release or reject raw materials and intermediate products, if necessary;
- to release or reject packaging and labelling materials and the final containers in which drugs are to be placed;
- to release or reject each lot of finished preparation;
- to evaluate the adequacy of the conditions under which raw materials, intermediate products, and finished biological preparations are stored;
- to evaluate the quality and stability of finished products and, when necessary, of raw materials and intermediate products;
- to establish expiry dates on the basis of the validity period related to specified storage conditions;
- to establish and, when necessary, revise control procedures and specifications; and
- to be responsible for the examination of returned preparations to determine whether such preparations should be released, reprocessed or destroyed; adequate records of the distribution of such preparations should be maintained.

9.2 A manufacturer's quality control laboratory shall be separated from the production area and ideally should be in a separate building. The control laboratory should be designed and equipped and of such a size as to be a self-contained entity, with adequate provision for the storage of documents and samples, preparation of records and performance of the necessary tests.

9.3 In-process controls play a specially important role in ensuring the consistent quality of biological products. Tests that are crucial for quality control but that cannot be carried out on the finished product shall be performed at an appropriate stage of production.



## QUALITY ASSURANCE OF PHARMACEUTICALS

9.4 Performance of all qualitative and quantitative tests mentioned in the specifications for starting materials may be replaced by a system of certificates issued by the producer of the starting material, provided that:

- there is a history of reliable production,
- the producer is regularly audited, and
- at least one specific identity test is conducted by the manufacturer of the final product.

9.5 Samples of intermediate and final products shall be retained in sufficient amount and under appropriate storage conditions to allow the repetition or confirmation of a batch control. However, reference samples of certain starting materials, e.g. components of culture media, need not necessarily be retained.

9.6 Certain operations require the continuous monitoring of data during a production process, for example monitoring and recording of physical parameters during fermentation.

9.7 Special consideration needs to be given to the quality control requirements arising from production of biological products by continuous culture.

### Authors

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## References

1. Good manufacturing practices for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report*. Geneva, World Health Organization, 1992 (WHO Technical Report Series, No. 823), Annex 1.
2. *WHO Expert Committee on Biological Standardization. Forty-second report*. Geneva, World Health Organization, 1992 (WHO Technical Report Series, No. 822).
3. *Laboratory biosafety manual*, 2nd ed. Geneva, World Health Organization, 1993.
4. *Quality management for chemical safety testing*. Geneva, World Health Organization, 1992 (Environmental Health Criteria, No. 141).
5. *WHO Expert Committee on Biological Standardization. Fortieth report*. Geneva, World Health Organization, 1990 (WHO Technical Report Series, No. 800), Annex 1.

## Investigational pharmaceutical products for clinical trials in humans<sup>1</sup>

### 1. Introductory note

The legal status of investigational pharmaceutical products for human use varies from country to country; in some of them (e.g. Germany, the United States and others), these products are manufactured and inspected like “normal” licensed pharmaceutical products. In most other countries, however, they are not covered by legal and regulatory provisions in the areas of good manufacturing practice (GMP) inspection, etc.

However, the EC guide on GMP (1) recommends that the principles of GMP should be applied, as appropriate, to the preparation of these products, and the WHO guide on GMP, according to the statement in the general considerations, is applicable to “the preparation of clinical trials supplies” (2, page 18).

### 2. General considerations

The present guidelines supplement both the WHO guide on GMP and the guidelines on good clinical practice (GCP) for trials on pharmaceutical products (3). The application of the principles of GMP to the preparation of investigational products is necessary for several reasons:

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<sup>1</sup> Good manufacturing practices: supplementary guidelines for the manufacture of investigational pharmaceutical products for clinical trials in humans. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report*. Geneva, World Health Organization, 1996, Annex 7 (WHO Technical Report Series, No. 863).



## QUALITY ASSURANCE OF PHARMACEUTICALS

- To assure consistency between and within batches of the investigational product and thus assure the reliability of clinical trials.
- To assure consistency between the investigational product and the future commercial product and therefore the relevance of the clinical trial to the efficacy and safety of the marketed product.
- To protect subjects of clinical trials from poor-quality products resulting from manufacturing errors (omission of critical steps such as sterilization, contamination and cross-contamination, mix-ups, wrong labelling, etc.), or from starting materials and components of inadequate quality.
- To document all changes in the manufacturing process.

In this context, the selection of an appropriate dosage for clinical trials is important. While it is accepted that in early trials the dosage form may be very different from the anticipated final formulation (e.g. a capsule instead of a tablet), in the pivotal Phase III studies it should be similar to the projected commercial presentation; otherwise these trials will not necessarily prove that the marketed product is both efficacious and safe.

If there are significant differences between the clinical and commercial dosage forms, data should be submitted to the registration authorities to demonstrate that the final dosage form is equivalent, in terms of bioavailability and stability, to that used in the clinical trials. Final manufacturing methods must be revalidated following changes in processes, scaling-up, transfer to other manufacturing sites, etc.

This Annex specifically addresses those practices that may be different for investigational products, which are usually not manufactured in accordance with a set routine, and which may possibly be incompletely characterized during the initial stages of clinical development.

### 3. Glossary

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

#### *clinical trial*

Any systematic study on pharmaceutical products in human subjects, whether in patients or other volunteers, in order to discover or verify the effects of, and/or identify any adverse reaction to, investigational products, and/or to study the absorption, distribution, metabolism and excretion of the products with the object of ascertaining their efficacy and safety.

Clinical trials are generally divided into Phases I–IV. It is not possible to draw clear distinctions between these phases, and different opinions about details and methodology do exist. However, the individual phases, based on their purposes as related to the clinical development of pharmaceutical products, can be briefly defined as follows:



*Phase I.* These are the first trials of a new active ingredient or new formulations in humans, often carried out in healthy volunteers. Their purpose is to make a preliminary evaluation of safety, and an initial pharmacokinetic/pharmacodynamic profile of the active ingredient.

*Phase II.* The purpose of these therapeutic pilot studies is to determine activity and to assess the short-term safety of the active ingredient in patients suffering from a disease or condition for which it is intended. The trials are performed in a limited number of subjects and are often, at a later stage, of a comparative (e.g. placebo-controlled) design. This phase is also concerned with the determination of appropriate dose ranges/regimens and (if possible) the clarification of dose-response relationships in order to provide an optimal background for the design of extensive therapeutic trials.

*Phase III:* This phase involves trials in large (and possibly varied) patient groups for the purpose of determining the short- and long-term safety-efficacy balance of formulation(s) of the active ingredient, and assessing its overall and relative therapeutic value. The pattern and profile of any frequent adverse reactions must be investigated, and special features of the product must be explored (e.g. clinically relevant drug interactions, factors leading to differences in effect, such as age). The trials should preferably be randomized double-blind, but other designs may be acceptable, e.g. long-term safety studies. In general, the conditions under which the trials are conducted should be as close as possible to the normal conditions of use.

*Phase IV.* In this phase studies are performed after the pharmaceutical product has been marketed. They are based on the product characteristics on which the marketing authorization was granted and normally take the form of post-marketing surveillance, and assessment of therapeutic value or treatment strategies. Although methods may differ, the same scientific and ethical standards should apply to Phase IV studies as are applied in premarketing studies. After a product has been placed on the market, clinical trials designed to explore new indications, new methods of administration or new combinations, etc., are normally regarded as trials of new pharmaceutical products.

*investigational product*

Any pharmaceutical product (new product or reference product) or placebo being tested or used as a reference in a clinical trial.

*investigator*

The person responsible for the trial and for protecting the rights, health and welfare of the subjects in the trial. The investigator must be an appropriately qualified person legally allowed to practise medicine/dentistry.

*monitor*

A person appointed by, and responsible to, the sponsor for monitoring and reporting the progress of the trial and for the verification of data.



## QUALITY ASSURANCE OF PHARMACEUTICALS

### *order*

An instruction to process, package and/or ship a certain number of units of an investigational product.

### *pharmaceutical product*

For the purpose of this Annex, this term is defined in the same way as in the WHO guidelines on GCP (3), i.e. as any substance or combination of substances which has a therapeutic, prophylactic or diagnostic purpose, or is intended to modify physiological functions, and is presented in a dosage form suitable for administration to humans.

### *product specification file(s)*

Reference file(s) containing all the information necessary to draft the detailed written instructions on processing, packaging, labelling, quality control testing, batch release, storage conditions and shipping.

### *protocol*

A document which gives the background, rationale and objectives of the trial and describes its design, methodology and organization, including statistical considerations, and the conditions under which it is to be performed and managed. It should be dated and signed by the investigator/institution involved and the sponsor, and can, in addition, function as a contract.

### *shipping/dispatch*

The assembly, packing for shipment, and sending of ordered medicinal products for clinical trials.

### *sponsor*

An individual, company, institution or organization which takes responsibility for the initiation, management and/or financing of a clinical trial. When an investigator independently initiates and takes full responsibility for a trial, the investigator then also assumes the role of the sponsor.

## 4. Quality assurance

Quality assurance of pharmaceutical products has been defined and discussed in detail in the guide on GMP (2, pages 25–26).

The quality of dosage forms in Phase III clinical studies should be characterized and assured at the same level as for routinely manufactured products. The quality assurance system, designed, established and verified by the manufacturer, should be described in writing, taking into account the GMP principles to the extent that they are applicable to the operations in question. This system should also cover the interface between the manufacture and the trial site (e.g. shipment, storage, occasional additional labelling).



## 5. Validation<sup>1</sup>

Some of the production processes for investigational products that have not received marketing authorization may not be validated to the extent necessary for a routine production operation. The product specifications and manufacturing instructions may vary during development. This increased complexity in the manufacturing operations requires a highly effective quality assurance system.

For sterile products, there should be no reduction in the degree of validation of sterilizing equipment required. Validation of aseptic processes presents special problems when the batch size is small, since the number of units filled may be not adequate for a validation exercise. Filling and sealing, which is often done by hand, can compromise the maintenance of sterility. Greater attention should therefore be given to environmental monitoring.

## 6. Complaints

The conclusions of any investigation carried out in response to a complaint should be discussed between the manufacturer and the sponsor (if different) or between the persons responsible for manufacture and those responsible for the relevant clinical trial in order to assess any potential impact on the trial and on the product development, to determine the cause, and to take any necessary corrective action.

## 7. Recalls

Recall procedures should be understood by the sponsor, investigator and monitor in addition to the person(s) responsible for recalls, as described in the guide on GMP (2, pages 28–29).

## 8. Personnel

Although it is likely that the number of staff involved will be small, people should be separately designated as responsible for production and quality control. All production operations should be carried out under the control of a clearly identified responsible person. Personnel concerned with development, involved in production and quality control, need to be instructed in the principles of GMP.

## 9. Premises and equipment

During the manufacture of investigational products, different products may be handled in the same premises and at the same time, and this reinforces the need

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<sup>1</sup> For additional advice on validation, see *Validation of manufacturing processes*, pp. 53–71.



## QUALITY ASSURANCE OF PHARMACEUTICALS

to eliminate all risks of contamination, including cross-contamination. Special attention should be paid to line clearance in order to avoid mix-ups. Validated cleaning procedures should be followed to prevent cross-contamination.

For the production of the particular products referred to in section 11.20 of the guide on GMP (2, page 38), campaign working may be acceptable in place of dedicated and self-contained facilities. Because the toxicity of the materials may not be fully known, cleaning is of particular importance; account should be taken of the solubility of the product and excipients in various cleaning agents.

### 10. Materials

#### Starting materials

The consistency of production may be influenced by the quality of the starting materials. Their physical, chemical and, when appropriate, microbiological properties should therefore be defined, documented in their specifications, and controlled. Existing compendial standards, when available, should be taken into consideration. Specifications for active ingredients should be as comprehensive as possible, given the current state of knowledge. Specifications for both active and non-active ingredients should be periodically reassessed.

Detailed information on the quality of active and non-active ingredients, as well as of packaging materials, should be available so as to make it possible to recognize and, as necessary, allow for any variation in production.

#### Chemical and biological reference standards for analytical purposes

Reference standards from reputable sources (WHO or national standards) should be used, if available; otherwise the reference substance(s) for the active ingredient(s) should be prepared, tested and released as reference material(s) by the producer of the investigational pharmaceutical product, or by the producer of the active ingredient(s) used in the manufacture of that product.

#### Principles applicable to reference products for clinical trials

In studies in which an investigational product is compared with a marketed product, steps should be taken to ensure the integrity and quality of the reference products (final dosage form, packaging materials, storage conditions, etc.). If significant changes are to be made in the product, data should be available (e.g. on stability, comparative dissolution) that demonstrate that these changes do not influence the original quality characteristics of the product.





## 11. Documentation

Specifications (for starting materials, primary packaging materials, intermediate and bulk products and finished products), master formulae, and processing and packaging instructions may be changed frequently as a result of new experience in the development of an investigational product. Each new version should take into account the latest data and include a reference to the previous version so that traceability is ensured. Rationales for changes should be stated and recorded.

Batch processing and packaging records should be retained for at least 2 years after the termination or discontinuance of the clinical trial, or after the approval of the investigational product.

### Order

The order may request the processing and/or packaging of a certain number of units and/or their shipping. It may only be given by the sponsor to the manufacturer of an investigational product. It should be in writing (though it may be transmitted by electronic means), precise enough to avoid any ambiguity and formally authorized, and refer to the approved product specification file (see below).

### Product specification file(s)

A product specification file (or files) should contain the information necessary to draft the detailed written instructions on processing, packaging, quality control testing, batch release, storage conditions and/or shipping. It should indicate who has been designated or trained as the authorized person responsible for the release of batches (see reference 2, page 18). It should be continuously updated while at the same time ensuring appropriate traceability to the previous versions.

### Specifications

In developing specifications, special attention should be paid to characteristics which affect the efficacy and safety of pharmaceutical products, namely:

- The accuracy of the therapeutic or unitary dose: homogeneity, content uniformity.
- The release of active ingredients from the dosage form: dissolution time, etc.
- The estimated stability, if necessary, under accelerated conditions, the preliminary storage conditions and the shelf-life of the product.<sup>1</sup>

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<sup>1</sup> See *Quality assurance of pharmaceuticals: a compendium of guidelines and related materials. Vol. 1.* Geneva, World Health Organization, 1997:46–61.



## QUALITY ASSURANCE OF PHARMACEUTICALS

In addition, the package size should be suitable for the requirements of the trial.

Specifications may be subject to change as the development of the product progresses. Changes should, however, be made in accordance with a written procedure authorized by a responsible person and clearly recorded. Specifications should be based on all available scientific data, current state-of-the-art technology, and the regulatory and pharmacopoeial requirements.

### Master formulae and processing instructions

These may be changed in the light of experience, but allowance must be made for any possible repercussions on stability and, above all, on bioequivalence between batches of finished products. Changes should be made in accordance with a written procedure, authorized by a responsible person and clearly recorded.

It may sometimes not be necessary to produce master formulae and processing instructions, but for every manufacturing operation or supply there should be clear and adequate written instructions and written records. Records are particularly important for the preparation of the final version of the documents to be used in routine manufacture.

### Packaging instructions

The number of units to be packaged should be specified before the start of the packaging operations. Account should be taken of the number of units necessary for carrying out quality controls and of the number of samples from each batch used in the clinical trial to be kept as a reference for further rechecking and control. A reconciliation should be carried out at the end of the packaging and labelling process.

### Labelling instructions

The information presented on labels should include:

- The name of the sponsor.
- A statement: “for clinical research use only”.
- A trial reference number.
- A batch number.
- The patient identification number.<sup>1</sup>
- The storage conditions.
- The expiry date (month/year) or a retest date.

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<sup>1</sup> This is not necessarily inserted at the manufacturing facility but may be added at a later stage.



Additional information may be displayed in accordance with the order (e.g. dosing instructions, treatment period, standard warnings). When necessary for blinding purposes, the batch number may be provided separately (see also “Blinding operations” on p. 137). A copy of each type of label should be kept in the batch packaging record.

### Processing and packaging batch records

Processing and packaging batch records should be kept in sufficient detail for the sequence of operations to be accurately traced. They should contain any relevant remarks which increase existing knowledge of the product, allow improvements in the manufacturing operations, and justify the procedures used.

### Coding (or randomization) systems

Procedures should be established for the generation, distribution, handling and retention of any randomization code used in packaging investigational products.

A coding system should be introduced to permit the proper identification of “blinded” products. The code, together with the randomization list, must permit proper identification of the product, including any necessary traceability to the codes and batch number of the product before the blinding operation. The coding system must permit determination without delay in an emergency situation of the identity of the actual treatment product received by individual subjects.

## 12. Production

Products intended for use in clinical trials (late Phase II and Phase III studies) should as far as possible be manufactured at a licensed facility, e.g.:

- A pilot plant, primarily designed and used for process development.
- A small-scale facility (sometimes called a “pharmacy”)<sup>1</sup> separate both from the company’s pilot plant and from routine production.
- A larger-scale production line assembled to manufacture materials in larger batches, e.g. for late Phase III trials and first commercial batches.
- The normal production line used for licensed commercial batches, and sometimes for the production of investigational pharmaceutical products if the number, e.g. of ordered ampoules, tablets or other dosage forms, is large enough.

The relation between the batch size for investigational pharmaceutical products manufactured in a pilot plant or small-scale facility to the planned full-size batches

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<sup>1</sup> Some manufacturers use the term “pharmacy” to designate other types of premises, e.g. areas where starting materials are dispensed and batches compounded.



## QUALITY ASSURANCE OF PHARMACEUTICALS

may vary widely depending on the pilot plant or “pharmacy” batch size demanded and the capacity available in full-size production.

The present guidelines are applicable to licensed facilities of the first and second types. It is easier to assure compliance with GMP in facilities of the second type, since processes are kept constant in the course of production and are not normally changed for the purpose of process development. Facilities of the remaining types should be subject to all GMP rules for pharmaceutical products.

Administratively, the manufacturer has yet another possibility, namely to contract out the preparation of investigational products. Technically, however, the licensed facility will be of one of the above-mentioned types. The contract must then clearly state, inter alia, the use of the pharmaceutical product(s) in clinical trials. Close cooperation between the contracting parties is essential.

### Manufacturing operations

Validated procedures may not always be available during the development phase, which makes it difficult to know in advance what critical parameters and in-process controls would help to control these parameters. Provisional production parameters and in-process controls may then usually be deduced from experience with analogous products. Careful consideration by key personnel is called for in order to formulate the necessary instructions and to adapt them continuously to the experience gained in production.

For sterile investigational products, assurance of sterility should be no less than for licensed products. Cleaning procedures should be appropriately validated and designed in the light of the incomplete knowledge of the toxicity of the investigational product. Where processes such as mixing have not been validated, additional quality control testing may be necessary.

### Packaging and labelling

The packaging and labelling of investigational products are likely to be more complex and more liable to errors (which are also harder to detect) when “blinded” labels are used than for licensed products. Supervisory procedures such as label reconciliation, line clearance, etc., and the independent checks by quality control staff should accordingly be intensified.

The packaging must ensure that the investigational product remains in good condition during transport and storage at intermediate destinations. Any opening of, or tampering with, the outer packaging during transport should be readily discernible.



## Blinding operations

In the preparation of “blinded” products, in-process control should include a check on the similarity in appearance and any other required characteristics of the different products being compared.

### 13. Quality control

As processes may not be standardized or fully validated, end-product testing is more important in ensuring that each batch meets its specification.

Product release is often carried out in two stages, before and after final packaging:<sup>1</sup>

1. Bulk product assessment: this should cover all relevant factors, including production conditions, the results of in-process testing, a review of manufacturing documentation and compliance with the product specification file and the order.
2. Finished product assessment: this should cover, in addition to the bulk product assessment, all relevant factors, including packaging conditions, the results of in-process testing, a review of packaging documentation and compliance with the product specification file and the order.

When necessary, quality control should also be used to verify the similarity in appearance and other physical characteristics, odour, and taste of “blinded” investigational products.

Samples of each batch of product should be retained in the primary container used for the study or in a suitable bulk container for at least 2 years after the termination or completion of the relevant clinical trial. If the sample is not stored in the pack used for the study, stability data should be available to justify the shelf-life in the pack used.

### 14. Shipping, returns, and destruction

The shipping, return and destruction of unused products should be carried out in accordance with the written procedures laid down in the protocol. All unused products sent outside the manufacturing plant should, as far as possible, either be returned to the manufacturer or destroyed in accordance with clearly defined instructions.

#### Shipping

Investigational products should be shipped in accordance with the orders given by the sponsor.

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<sup>1</sup> This practice also exists at certain large companies with regard to licensed products.



## QUALITY ASSURANCE OF PHARMACEUTICALS

A shipment is sent to an investigator only after the following two-step release procedure: (i) the release of the product after quality control (“technical green light”); and (ii) the authorization to use the product, given by the sponsor (“regulatory green light”). Both releases should be recorded.

The sponsor should ensure that the shipment will be received and acknowledged by the correct addressee as stated in the protocol.

A detailed inventory of the shipments made by the manufacturer should be maintained, and should make particular mention of the addressee’s identification.

### Returns

Investigational products should be returned under agreed conditions defined by the sponsor, specified in written procedures, and approved by authorized staff members.

Returned investigational products should be clearly identified and stored in a dedicated area. Inventory records of returned medicinal products should be kept. The responsibilities of the investigator and the sponsor are dealt with in greater detail in the WHO guidelines on GCP (3).

### Destruction

The sponsor is responsible for the destruction of unused investigational products, which should therefore not be destroyed by the manufacturer without prior authorization by the sponsor. Destruction operations should be carried out in accordance with environmental safety requirements.

Destruction operations should be recorded in such a manner that all operations are documented. The records should be kept by the sponsor.

If requested to destroy products, the manufacturer should deliver a certificate of destruction or a receipt for destruction to the sponsor. These documents should permit the batches involved to be clearly identified.

### References

1. *Good manufacturing practice for medicinal products in the European Community*. Brussels, Commission of the European Communities, 1992.
2. Good manufacturing practices for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report*. Geneva, World Health Organization, 1992:14–79 (WHO Technical Report Series, No. 823).
3. Guidelines for good clinical practice (GCP) for trials on pharmaceutical products. In: *The use of essential drugs. Model List of Essential Drugs (Eighth List). Sixth report of the WHO Expert Committee*. Geneva, World Health Organization, 1995:97–137 (WHO Technical Report Series, No. 850).



## Herbal medicinal products<sup>1,2</sup>

### 1. Glossary

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

*constituents with known therapeutic activity*

Substances or groups of substances which are chemically defined and known to contribute to the therapeutic activity of a plant material or of a preparation.

*herbal medicinal product*

Medicinal product containing, as active ingredients, exclusively plant material and/or preparations. This term is generally applied to a finished product. If it refers to an unfinished product, this should be indicated.

*markers*

Constituents of a medicinal plant material which are chemically defined and of interest for control purposes. Markers are generally employed when constituents of known therapeutic activity are not found or are uncertain, and may be used to calculate the quantity of plant material or preparation in the finished product. When starting materials are tested, markers in the plant material or preparation must be determined quantitatively.

*medicinal plant*

A plant (wild or cultivated) used for medicinal purposes.

*medicinal plant material (crude plant material, vegetable drug)*

Medicinal plants or parts thereof collected for medicinal purposes.

*plant preparations*

Comminuted or powdered plant material, extracts, tinctures, fatty or essential oils, resins, gums, balsams, expressed juices, etc., prepared from plant material, and preparations whose production involves a fractionation, purification or concentration process, but excluding chemically defined isolated constituents. A plant preparation can be regarded as the active ingredient whether or not the constituents having therapeutic activities are known.

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<sup>1</sup> Guidelines for the assessment of herbal medicines are provided in *Quality assurance of pharmaceuticals: a compendium of guidelines and related materials. Vol. 1*. Geneva, World Health Organization, 1997:31–37.

<sup>2</sup> Good manufacturing practices: supplementary guidelines for the manufacture of herbal medicinal products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report*. Geneva, World Health Organization, 1996, Annex 8 (WHO Technical Report Series, No. 863).



## 2. General

Unlike conventional pharmaceutical products, which are usually prepared from synthetic materials by means of reproducible manufacturing techniques and procedures, herbal medicinal products are prepared from material of plant origin which may be subject to contamination and deterioration, and may vary in composition and properties. Furthermore, in the manufacture and quality control of herbal medicinal products, procedures and techniques are often used which are substantially different from those employed for conventional pharmaceutical products.

The control of the starting materials, storage and processing assumes particular importance because of the often complex and variable nature of many herbal medicinal products and the number and the small quantity of defined active ingredients present in them.

## 3. Premises

### Storage areas

Medicinal plant materials should be stored in separate areas. The storage area should be well ventilated and equipped in such a way as to protect against the entry of insects or other animals, especially rodents. Effective measures should be taken to limit the spread of animals and microorganisms introduced with the plant material and to prevent cross-contamination. Containers should be located in such a way as to allow free air circulation.

Special attention should be paid to the cleanliness and good maintenance of the storage areas, particularly when dust is generated.

The storage of plants, extracts, tinctures and other preparations may require special conditions of humidity and temperature or protection from light; steps should be taken to ensure that these conditions are provided and monitored.

### Production area

To facilitate cleaning and to avoid cross-contamination whenever dust is generated, special precautions should be taken during the sampling, weighing, mixing and processing of medicinal plants, e.g. by the use of dust extraction or dedicated premises.

## 4. Documentation

### Specifications for starting materials

In addition to the data called for in sections 14 and 18 of “Good manufacturing practices for pharmaceutical products”(1), the specifications for medicinal plant materials should as far as possible include the following:





- The botanical name, with reference to the authors.
- Details of the source of the plant (country or region of origin, and where applicable, method of cultivation, time of harvesting, collection procedures, possible pesticides used, etc.).
- Whether the whole plant or only a part is used.
- When dried plant is purchased, the drying system.
- A description of the plant material based on visual and/or microscopical inspection.
- Suitable identification tests including, where appropriate, identification tests for known active ingredients or markers.
- The assay, where appropriate, of constituents of known therapeutic activity or markers.
- Suitable methods for the determination of possible pesticide contamination and the acceptable limits for such contamination.
- The results of tests for toxic metals and for likely contaminants, foreign materials, and adulterants.
- The results of tests for microbial contamination and aflatoxins.

Any treatment used to reduce fungal/microbial contamination or other infestation should be documented. Instructions on the conduct of such procedures should be available and should include details of the process, tests and limits for residues.

### Qualitative and quantitative requirements

These should be expressed in the following ways:

1. Medicinal plant material:
  - (a) the quantity of plant material must be stated; or
  - (b) the quantity of plant material may be given as a range, corresponding to a defined quantity of constituents of known therapeutic activity.

Example:

<i>Name of active ingredient</i>	<i>Quantity</i>
Sennae folium	(a) 900 mg or (b) 830–1000 mg, corresponding to 25 mg of hydroxyanthracene glycosides, calculated as sennoside B

2. Plant preparation:
  - (a) the equivalent quantity or the ratio of plant material to plant preparation must be stated (this does not apply to fatty or essential oils); or
  - (b) the quantity of the plant preparation may be given as a range, corresponding to a defined quantity of constituents with known therapeutic activity (see example).



## QUALITY ASSURANCE OF PHARMACEUTICALS

The composition of any solvent or solvent mixture used and the physical state of the extract must be indicated.

If any other substance is added during the manufacture of the plant preparation to adjust the level of constituents of known therapeutic activity, or for any other purpose, the added substance(s) must be described as “other ingredients” and the genuine extract as the “active ingredient”.

Example:

<i>Name of active ingredient</i>	<i>Quantity</i>
Sennae folium	(a) 125 mg ethanolic extract (8:1) or 125 mg ethanolic extract, equivalent to 1000 mg of Sennae folium or (b) 100–130 mg ethanolic extract (8:1), corresponding to 25 mg of hydroxyanthracene glycosides, calculated as sennoside B
<i>Other ingredient</i>	
Dextrin	20–50 mg

### Specifications for the finished product

The control tests for the finished product must be such as to allow the qualitative and quantitative determination of the active ingredients. If the therapeutic activity of constituents is known, this must be specified and determined quantitatively. When this is not feasible, specifications must be based on the determination of markers.

If either the final product or the preparation contains several plant materials and a quantitative determination of each active ingredient is not feasible, the combined content of several active ingredients may be determined. The need for such a procedure must be justified.

### Processing instructions

The processing instructions should list the different operations to be performed on the plant material, such as drying, crushing and sifting, and also include the temperatures required in the drying process, and the methods to be used to control fragments or particle size. Instructions on sieving or other methods of removing foreign materials should also be given. Details of any process, such as fumigation, used to reduce microbial contamination, together with methods of determining the extent of such contamination, should also be given.

For the production of plant preparations, the instructions should specify any vehicle or solvent that may be used, the times and temperatures to be observed during extraction, and any concentration methods that may be required.



## 5. Quality control

The personnel of quality control units should have particular expertise in herbal medicinal products to be able to carry out identification tests, and check for adulteration, the presence of fungal growth or infestations, lack of uniformity in a consignment of medicinal plant materials, etc.

Reference samples of plant materials must be available for use in comparative tests, e.g. visual and microscopic examination and chromatography.

### Sampling

Sampling must be carried out with special care by personnel with the necessary expertise since medicinal plant materials are composed of individual plants or parts of plants and are therefore heterogeneous to some extent.

Further advice on sampling, visual inspection, analytical methods, etc., is given in *Quality control methods for medicinal plant materials* (2).

## 6. Stability tests

It will not be sufficient to determine the stability only of the constituents with known therapeutic activity, since plant materials or plant preparations in their entirety are regarded as the active ingredient. It must also be shown, as far as possible, e.g. by comparisons of chromatograms, that the other substances present are stable and that their content as a proportion of the whole remains constant.

If a herbal medicinal product contains several plant materials or preparations of several plant materials, and it is not feasible to determine the stability of each active ingredient, the stability of the product should be determined by methods such as chromatography, widely used assay methods, and physical and sensory or other appropriate tests.

## References

1. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report.* Geneva, World Health Organization, 1992:44–52; 75–76 (WHO Technical Report Series, No. 823).
2. *Quality control methods for medicinal plant materials.* Geneva, World Health Organization, 1992 (unpublished document WHO/PHARM/92.559/rev. 1; available on request from Health Technology and Pharmaceuticals, World Health Organization, 1211 Geneva 27, Switzerland).



## Radiopharmaceutical products<sup>1</sup>

1. Scope of these guidelines	130
2. Principles	131
3. Personnel	131
4. Premises and equipment	132
5. Production	133
6. Labelling	134
7. Production and distribution records	136
8. Quality assurance and quality control	136
Acknowledgements	138
References	138

### 1. Scope of these guidelines

These guidelines are intended to complement those already available for pharmaceutical products (1,2) as well as those for sterile pharmaceutical products (3).

The regulatory procedures necessary to control radiopharmaceutical products are in large part determined by the sources of these products and the methods of manufacture. Manufacturing procedures within the scope of these guidelines include:

- The preparation of radiopharmaceuticals in hospital radiopharmacies.
- The preparation of radiopharmaceuticals in centralized radiopharmacies.
- The production of radiopharmaceuticals in nuclear centres and institutes or by industrial manufacturers.
- The preparation and production of radiopharmaceuticals in positron emission tomography (PET) centres.

Radiopharmaceuticals can be classified into four categories:

1. Ready-for-use radioactive products.
2. Radionuclide generators.
3. Non-radioactive components (“kits”) for the preparation of labelled compounds with a radioactive component (usually the eluate from a radionuclide generator).
4. Precursors used for radiolabelling other substances before administration (e.g. samples from patients).

Radiopharmaceutical products include inorganic compounds, organic compounds, peptides, proteins, monoclonal antibodies and fragments, and oligonucleotides labelled with radionuclides with half-lives from a few seconds to several days.

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<sup>1</sup> Ref.: WHO Technical Report Series, No 908, 2003, Annex 3, pp. 26–35



## 2. Principles

Radiopharmaceuticals must be manufactured in accordance with the basic principles of good manufacturing practices (GMP). The matters covered by these guidelines should therefore be considered as supplementary to the general requirements for GMP previously published (1,2) and relate specifically to the production and control of radiopharmaceuticals. In the preparation of these guidelines, due consideration was given to national or international radiation safety guidelines (4).

Because of their short half-lives, many radiopharmaceuticals are released and administered to patients shortly after their production, so that quality control may sometimes be retrospective. Strict adherence to GMP is therefore mandatory.

## 3. Personnel

3.1 The manufacturing establishment, whether a hospital radiopharmacy, centralized radiopharmacy, nuclear centre or institution, industrial manufacturer or PET centre, and its personnel should be under the control of a person who has a proven record of academic achievement together with a demonstrated level of practical expertise and experience in radiopharmacy and radiation hygiene. Supporting academic and technical personnel should have the necessary postgraduate or technical training and experience appropriate to their function.

3.2 Personnel required to work in radioactive, clean and aseptic areas should be selected with care, to ensure that they can be relied on to observe the appropriate codes of practice and are not subject to any disease or condition that could compromise the integrity of the product. Health checks on personnel should be requested before employment and periodically thereafter. Any changes in personal health status (e.g. in haematology) may require the temporary exclusion of the person from further radiation exposure.

3.3 Only the minimum number of personnel required should be present in clean and aseptic areas when work is in progress. Access to these areas should be restricted during the preparation of radiopharmaceuticals, kits or sterile set-ups. Inspection and control procedures should be conducted from outside these areas as far as possible.

3.4 During the working day, personnel may pass between radioactive and non-radioactive areas only if the safety rules of radiation control (health physics control) are respected.

3.5 The release of a batch may be approved only by a pharmacist or a person with academic qualifications officially registered as a suitably qualified person, and with appropriate experience in the manufacture of radiopharmaceuticals.

3.6 To ensure the safe manufacture of radiopharmaceuticals, personnel should be trained in GMP, the safe handling of radioactive materials and radiation safety



## QUALITY ASSURANCE OF PHARMACEUTICALS

procedures. They should also be required to take periodic courses and receive training to keep abreast of the latest developments in their fields.

3.7 Training records should be maintained and periodic assessments of the effectiveness of training programmes should be made.

3.8 All personnel engaged in production, maintenance and testing should follow the relevant guidelines for handling radioactive products and be monitored for possible contamination and/or irradiation exposure.

### **4. Premises and equipment**

4.1 As a general principle, buildings must be located, designed, constructed, adapted and maintained to suit the operations to be carried out within them. Laboratories for the handling of radioactive materials must be specially designed to take into consideration aspects of radiation protection in addition to cleanliness and sterility. Interior surfaces (walls, floors and ceilings) should be smooth, impervious and free from cracks; they should not shed matter and should permit easy cleaning and decontamination. Drains should be avoided wherever possible and, unless essential, should be excluded from aseptic areas.

4.2 Specific disposal systems should be mandatory for radioactive effluents. These systems should be effectively and carefully maintained to prevent contamination and exposure of personnel to the radioactive waste both within and outside the facility.

4.3 Sinks should be excluded from aseptic areas. Any sink installed in other clean areas should be of suitable material and be regularly sanitized. Adequate precautions should be taken to avoid contamination of the drainage system with radioactive effluents.

4.4 Lighting, heating, ventilation and, if necessary, air-conditioning should be designed to maintain a satisfactory temperature and relative humidity to ensure the comfort of personnel working in protective clothing. Buildings should be in a good state of repair. The condition of the buildings should be reviewed regularly and repairs carried out when and where necessary. Special care should be exercised to ensure that building repair or maintenance operations do not compromise products. Premises should provide sufficient space for the operations to be carried out, allowing an efficient flow of work and effective communication and supervision. All buildings and rooms should be clean, sanitary and free from radioactive contamination.

4.5 Ventilation of radiopharmaceutical production facilities should meet the requirement to prevent the contamination of products and the exposure of working personnel to radioactivity. Suitable pressure and airflow patterns should be maintained by appropriate isolation/enveloping methods. Air handling systems for both radioactive and non-radioactive areas should be fitted with



alarms so that the working personnel in the laboratory are warned of any failure of these systems.

4.6 Dedicated facilities and equipment should be used for the manufacture of any radiopharmaceutical product derived from human blood or plasma. Autoclaves used in production areas for radiopharmaceuticals may be placed behind a lead shield to minimize the radiation exposure of the operators. Such autoclaves should be checked for contamination immediately after use to minimize the possibility of cross-contamination by radioactivity of the products in the next autoclave cycles.

4.7 All containers of radiopharmaceutical substances, regardless of the stage of manufacture, should be identified by securely attached labels. Cross-contamination should be prevented by the adoption of some or all of the following measures:

- processing and filling in segregated areas;
- avoiding the manufacture of different products at the same time, unless they are effectively segregated;
- containing material transfer by means of airlocks, air extraction, changing clothes and careful washing and decontamination of equipment;
- protecting against the risks of contamination caused by recirculation of untreated air, or by accidental re-entry of extracted air;
- using “closed systems” of manufacture;
- taking care to prevent aerosol formation;
- using sterilized containers.

4.8 Positive pressure areas should be used to process sterile products. In general, any radioactivity should be handled within specifically designed areas maintained under negative pressures. The production of sterile radioactive products should therefore be carried out under negative pressure surrounded by a positive pressure zone ensuring that appropriate air quality requirements are met.

4.9 Separate air-handling units should be used for radioactive and non-radioactive areas. Air from operations involving radioactivity should be exhausted through appropriate filters that are regularly checked for performance.

4.10 Pipework, valves and vent filters should be properly designed to facilitate validated cleaning and decontamination.

## 5. Production

5.1 Standard operating procedures (SOPs) must be available for all operating procedures and should be regularly reviewed and kept up to date for all manufacturing operations. All entries on batch records should be initiated by the operator and independently checked by another operator or supervisor.



## QUALITY ASSURANCE OF PHARMACEUTICALS

5.2 Specifications for starting materials should include details of their source, origin and (where applicable) method of manufacture and of the controls used to ensure their suitability for use. Release of a finished product should be conditional on satisfactory results being obtained in the tests on starting materials.

5.3 Careful consideration should be given to the validation of sterilization methods.

5.4 A wide variety of equipment is used in the preparation of radiopharmaceuticals. Equipment for chromatography should, in general, be dedicated to the preparation and purification of one or several products labelled with the same radionuclide to avoid radioactive cross-contamination. The life span of columns should be defined. Great care should be taken in cleaning, sterilizing and operating freeze-drying equipment used for the preparation of kits.

5.5 A list of critical equipment should be drawn up, including any equipment such as a balance, pyrogen oven, dose calibrator, sterilizing filter, etc., where an error in the reading or function could potentially cause harm to the patient being given the final product. These devices should be calibrated or tested at regular intervals and should be checked daily or before production is started. The results of these tests should be included in the daily production records.

5.6 Specific equipment for radioactive measurements may be required as well as radioactive reference standards. For the measurement of very short half-lives, national central laboratories should be contacted to calibrate the apparatus. Where this is not possible, alternative approaches, such as documented procedures, may be used.

5.7 In the case of labelling kits, freeze drying should be carried out as an aseptic procedure. If an inert gas such as nitrogen is used to fill vials, it must be filtered to remove possible microbial contamination.

5.8 The dispensing, packaging and transportation of radiopharmaceuticals should comply with the relevant national regulations and international guidelines (5).

## 6. Labelling

6.1 All products should be clearly identified by labels, which must remain permanently attached to the containers under all storage conditions. An area of the container should be left uncovered to allow inspection of the contents. If the final container is not suitable for labelling, the label should appear on its package. Information on batch coding must be provided to the national and/or regional authorities.

6.2 The labels of radiopharmaceuticals must comply with the relevant national regulations and international agreements. For registered radiopharmaceuticals, the national control authority should approve the labels.





## SPECIFIC PHARMACEUTICAL PRODUCTS

6.3 The label on the container should show:

- (a) the name of the drug product and/or the product identification code;
- (b) the name of the radionuclide;
- (c) the name of the manufacturer or the company and/or the person responsible for placing the drug on the market;
- (d) the radioactivity per unit dose:
  - for liquid preparations, the total radioactivity in the container, or the radioactive concentration per millilitre, at a stated date and, if necessary, hour, and the volume of liquid in the container;
  - for solid preparations, such as freeze-dried preparations, the total radioactivity at a stated date and, if necessary, hour;
  - for capsules, the radioactivity of each capsule at a stated date and, if necessary, hour, and the number of capsules in the container;
  - where relevant, the international symbol for radioactivity.

6.4 The label on the package should state:

- (a) the qualitative and quantitative composition;
- (b) the radioactive isotopes and the amount of radioactivity at the time of dispatch;
- (c) the route of administration;
- (d) the expiry date;
- (e) any special storage conditions;
- (f) mandatory information related to transport regulations for radioactive materials.

6.5 The leaflet in the package should contain the specific product information and indications for use. This information is especially important for preparation kits (cold kits), and should include:

- (a) the name of the product and a description of its use;
- (b) the contents of the kit;
- (c) the identification and quality requirements concerning the radiolabelling materials that can be used to prepare the radiopharmaceutical, namely:
  - the directions for preparing the radiopharmaceutical, including the range of activity and the volume, together with a statement of the storage requirements for the prepared radiopharmaceutical;
  - a statement of the shelf-life of the prepared radiopharmaceutical;
  - the indications and contraindications (pregnancy, children, drug reactions, etc.) in respect of the prepared radiopharmaceutical;
  - warnings and precautions in respect of the components and the prepared radiopharmaceutical, including radiation safety aspects;



## QUALITY ASSURANCE OF PHARMACEUTICALS

- where applicable, the pharmacology and toxicology of the prepared radiopharmaceutical, including the route of elimination and the effective half-life;
- the radiation dose that a patient will receive from the prepared radiopharmaceutical;
- the precautions to be taken by users and patients during the preparation and administration of the product and the special precautions for the disposal of the container and any unconsumed portions;
- a statement of the recommended use of the prepared radiopharmaceutical and the recommended dosage;
- a statement of the route of administration of the prepared radiopharmaceutical;
- if appropriate for particular kits (i.e. those subject to variability beyond the recommended limits), the methods and specifications needed to check radiochemical purity.

### 7. Production and distribution records

7.1 The processing records of regular production batches must provide a complete account of the manufacturing history of each batch of a radiopharmaceutical, showing that it has been manufactured, tested, dispensed into containers and distributed in accordance with the written procedures.

7.2 Separate records for the receipt, storage, use and disposal of radioactive materials should be maintained in accordance with radiation protection regulations.

7.3 Distribution records should be kept. Since the return of radioactive products is not practical, the purpose of recall procedures for such products is to prevent their use rather than an actual return. If necessary, the return of radioactive products should be carried out in accordance with international and national transport regulations.

### 8. Quality assurance and quality control

8.1 Radiopharmaceuticals are nearly always used before all quality control testing (e.g. tests for sterility, endotoxin, radionuclidic purity, etc.) has been completed. The implementation of and compliance with the quality assurance programme are therefore essential.

8.2 Quality assurance and/or quality control should have the following principal responsibilities:

- (a) the preparation of detailed instructions for each test and analysis;
- (b) ensuring the adequate identification and segregation of test samples to avoid mix-ups and cross-contamination;



## SPECIFIC PHARMACEUTICAL PRODUCTS

- (c) ensuring that environmental monitoring and equipment and process validation are conducted as appropriate for evaluating the adequacy of the manufacturing conditions;
- (d) the release or rejection of starting materials and intermediate products;
- (e) the release or rejection of packaging and labelling materials;
- (f) the release or rejection of each batch of finished preparation;
- (g) the evaluation of the adequacy of the conditions under which the starting materials, intermediate products and finished radiopharmaceutical preparations are stored;
- (h) the evaluation of the quality and stability of the finished products and, when necessary, of the starting materials and intermediate products;
- (i) the establishment of expiry dates on the basis of the validity period related to specified storage conditions;
- (j) the establishment and revision of the control procedures and specifications;
- (k) assuming the responsibility for retaining samples of radiopharmaceutical products;
- (l) assuming the responsibility for keeping adequate records of the distribution of the radiopharmaceutical products.

8.3 Whenever the size of the establishment permits, quality assurance and quality control duties should be organized in separate groups. Quality assurance should also include the monitoring and validation of the production process.

8.4 A manufacturer's quality control laboratory should be separated from the production area. The control laboratory should be designed, equipped and of such a size as to be a self-contained entity, with adequate provision for the storage of documents and samples, the preparation of records and the performance of the necessary tests.

8.5 The performance of all qualitative and quantitative tests mentioned in the specifications for the starting materials may be replaced by a system of certificates issued by the supplier of these materials, provided that:

- (a) there is a history of reliable production;
- (b) the producer or supplier is regularly audited;
- (c) at least one specific identity test is conducted by the manufacturer of the finished radiopharmaceutical.

8.6 Samples of the intermediate and final products should be retained in sufficient amounts and under appropriate storage conditions to allow repeated testing or verification of a batch control. These samples should be kept for an appropriate period in accordance with the shelf-lives of the radioactive components concerned. However, this may sometimes not be applicable, e.g. for radiopharmaceuticals with a short half-life.

8.7 Sampling procedures may be adapted to the purpose of the sampling, the type of controls being applied, and the nature of the material being sampled (e.g.



## QUALITY ASSURANCE OF PHARMACEUTICALS

a small batch size and/or its radioactive content). The procedure should be described in a written protocol.

### Acknowledgements

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### References

1. Good manufacturing practices for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report*. Geneva, World Health Organization, 1992, Annex 1 (WHO Technical Report Series, No. 823).
2. *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Vol. 2. Good manufacturing practices and inspection*. Geneva, World Health Organization, 1999.
3. Good manufacturing practices for sterile pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report*. Geneva, World Health Organization, 2002, Annex 6 (WHO Technical Report Series, No. 902).
4. *International basic safety standards for protection against ionizing radiation and for the safety of radiation sources: a safety standard*. Vienna, International Atomic Energy Authority, 1996 (Safety Series, No. 115).
5. *Regulations for the safe transport of radioactive material*. Vienna, International Atomic Energy Authority, 1996 (IAEA Safety Requirements Safety Standards Series, No. TS-R-1, Revised).



# 4.

## Inspection

### Pre-approval inspections<sup>1</sup>

1. General	139
2. Glossary	139
3. Objectives	140
4. Priorities	141
5. Preparation for the inspection	141
6. Carrying out the inspection	142
7. Sample collection and testing	143
8. Follow-up regulatory/administrative decisions	144
References	145

#### 1. General

The advice provided here extends that given in the “Provisional guidelines on the inspection of pharmaceutical manufacturers” (1). The objectives of an inspection, as given in the introduction to the guidelines, are:

- to control and enforce compliance with general good manufacturing practices (GMP) (2); and
- to authorize the manufacture of specific pharmaceutical products, normally in response to a licensing application.

These guidelines are applicable mainly to inspections of the first type, whether performed as a condition for the issue of a manufacturing licence/authorization, or on a periodic, routine basis. They are essentially concerned with inspections of manufacturing and quality-control facilities conducted before a marketing authorization (product licence or registration) for a pharmaceutical product is granted.

#### 2. Glossary

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

*application*

A marketing authorization for a new drug application.

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<sup>1</sup> Ref. WHO Technical Report Series, No 902, 2002. Annex 7, pp. 94–100



## QUALITY ASSURANCE OF PHARMACEUTICALS

### *manufacturer*

A company that carries out at least one step of manufacture (2).

### *manufacture*

All operations concerned with the purchase of materials and products, production (including packaging), quality control, release, storage, the distribution of pharmaceutical products, and the related controls (2).

### *method validation/verification*

Method validation is conducted where non-compendial analytical methods are included in the application to confirm that the applicants' proposed analytical methods are suitable for regulatory purposes. A side-by-side comparison with a compendial method, if available, should be included. Method verification is conducted where the methods are compendial, to confirm whether the product as compounded can be analysed satisfactorily by the official method.

### *pre-approval batches*

Pilot or laboratory-scale batches, upon which the application is based, e.g. batches used for pivotal clinical trials and/or those used for bioavailability, bioequivalence and stability studies, and scale-up batches.

## 3. Objectives

Before any application is approved, it is necessary to determine whether all establishments participating in the manufacture of the finished dosage form are in compliance with GMP and the application commitments. Pre-approval inspections have the following specific objectives:

- Evaluation of the establishment's compliance with GMP requirements, particularly regarding proper environment, quality management, personnel, facilities and equipment.
- Evaluation of the procedures and controls implemented in the manufacture of the product (pre-approval batches), to determine whether they are in conformity with the application commitments.
- Audit of the completeness and accuracy of the manufacturing and testing information submitted with the application, and of the conformity of pre-approval batches with planned commercial batches (process validation protocol).
- The collection of samples for the validation or verification of the analytical methods included in the application.



## 4. Priorities

Pre-approval inspections are considered to be an important part of the application review and approval process. However, since this represents a considerable workload, inspections are not normally carried out routinely, but rather only in specific cases where non-compliance is possible. Thus inspections may be required for:

- new chemical entities;
- drugs of narrow therapeutic range, and drugs for serious conditions requiring an assured therapeutic response;
- products previously associated with serious adverse effects, complaints, recalls, etc.;
- products that are difficult to manufacture or test, or that are of doubtful stability (and therefore associated with the risk of defects);
- new applicants or manufacturers; and
- applications from manufacturers who have previously failed to comply with GMP or official quality specifications.

For other applications, the drug regulatory authority will rely on the results of recent inspections of the applicant's or manufacturer's facilities for the production of dosage forms similar to that of the proposed product.

## 5. Preparation for the inspection

An inspection team should, where possible, include analysts and other specialists, e.g. in pharmaceutical technology, or if available, persons with expertise in these fields, when needed. Team members may be assigned to inspect new operations or manufacturing sites associated with product failures. When possible, the analyst involved in the laboratory evaluation of the product under review should participate in the inspection. Pre-approval inspection is often carried out by a single inspector.

It is necessary to verify that the applicant holds an appropriate manufacturing authorization and that manufacturing is carried out in conformity with that authorization (licence).

An essential step in the review of applications is determining whether the commitments made by the manufacturer are reflected in actual practice. A review of the application information is also important in preparing for inspections of firms or processes with which the inspector is unfamiliar. The drug regulatory authority should provide inspectors with relevant information on the application. (Some countries request an additional copy of this information from applicants which is forwarded to the inspection team.) The information provided should include a copy of the manufacturing and controls section of the application, together with information relating to pre-approval batches.



Reasonable efforts should be made to conduct pre-approval inspections at the earliest possible opportunity, since unnecessary delays will prevent the timely review of applications. However, in some facilities the development or the manufacturing processes may not have been completed. In addition, changes may have occurred in the status of the application, e.g. major deficiencies in the application or the closure of an ancillary facility may affect the need for an inspection. In any case, the timing of the inspection should be coordinated between the inspectorate and the applicant.

For the inspection of major new facilities involving many applications, special coordination efforts are often beneficial.

When desirable, pre-approval inspections should be coordinated with the laboratory scheduled for method validation so as to enable it to participate in the inspection and in the collection of samples.

## 6. Carrying out the inspection

Emphasis should be placed on the evaluation of the manufacturing process, including data verification and the assessment of compliance with GMP. The production and control procedures described in the application must be compared with those used for the manufacture of pre-approval batches. If warranted by records of past label mix-ups, packaging and labelling control procedures should be evaluated. A programme of ongoing stability testing needs to be addressed.

The inspection team will determine whether the application provides the scientific data justifying full-scale production procedures and controls. The validation of pertinent manufacturing procedures, including equipment qualification, will also be evaluated.<sup>1</sup> However, inspectors should not recommend withholding approval of applications based on a lack of complete full-scale, multiple-batch validation of sterile and non-sterile processes, unless the data submitted in the application are found to be of questionable validity or completeness. It should be understood that full-scale validation may be completed after approval of the application, but before shipment of the first commercial batches. Nevertheless, certain data must be included in the application to demonstrate that the sterilization or aseptic fill process has been qualified. The inspection team is expected to audit the data to determine their authenticity, accuracy and completeness.

Investigational products are often produced in facilities other than those used for full-scale production (4). These facilities and the associated manufacturing and control procedures are not routinely inspected unless validation of the transfer of the methods from the “investigational” facilities to the full-scale facilities is lacking or questionable. The facilities may be periodically inspected when this is required by national legislation/regulation.

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<sup>1</sup> For details of recommended validation programmes, see reference 3.





All suppliers and manufacturers of starting materials used in the formulation of pre-approval batches should be identified. The physical characteristics and specifications of the drug substance should be reviewed. This is particularly important for solid oral dosage forms where the physical characteristics of the drug substance often affect uniformity, dissolution and absorption of the dose.

When a pharmaceutical manufacturer replaces the supplier or manufacturer of the drug substance used for the manufacture of the pre-approval batches by another supplier or manufacturer, the application should include data demonstrating that the dosage forms formulated with the drug substance from the two different sources are equivalent in terms of conformity with established specifications, including those given in the application. Specifications should also cover the physical characteristics of the drug substances.

The addition of any new drug substance and/or dosage form to a production environment must be carefully evaluated in terms of its impact on other products already under production. Any changes that may be necessary in the building and facility must be assessed for their effect on overall compliance with GMP requirements. For example, a new toxic, potent or highly sensitizing product may require additional measures against cross-contamination, and facilities already operating at full capacity may not have adequate space for additional products. The evaluation should also include an assessment of whether any change in the manufacturing authorization is necessary.

Laboratory equipment and procedures must be qualified and validated. Every pre-approval inspection should include an evaluation of laboratory controls and procedures, and a review of some of the raw data used to generate results. The authenticity and accuracy of the data used in the development of a test method should be reviewed.

The inspection team should pay special attention to any newly established facilities, newly installed equipment and/or new raw material suppliers. If unapproved facilities are in use, this should be reported immediately. Inspections of these facilities are not normally required.

## 7. Sample collection and testing

The pre-approval inspection may include the collection of samples for validation of the analytical methods. Normally the sample size should be sufficient for three full analyses. Unless otherwise indicated by the laboratory, samples of the following sizes may be taken, depending on the dosage form of the product:

- tablets and capsules: 300 units of production;
- injections (single component): 100 units of production;
- injections (combination): 100 units of production plus 10 samples of each component;
- oral powders for reconstitution: 10 units of production;
- oral liquids: 1 litre.



## QUALITY ASSURANCE OF PHARMACEUTICALS

It is important to collect, with the samples, the relevant manufacturer's analytical documentation, namely a copy of the analytical methods used by the inspected laboratory and the report of the analyses performed by the applicant on the batch sampled. A method validation report may be of some use in better understanding and reproducing the analytical methods. Problems encountered in the performance of the analyses may be resolved by an exchange of information between the applicant and the government laboratory.

Samples are tested in accordance with methods described in the application. If there are problems with the methods that require additional information from the applicant, the laboratory director must review the situation and decide whether the applicant should be contacted. The written request should be included in the documentation submitted to the review analyst.

Each method validation/verification report should contain the following:

- The identification of the test samples received, a description of the product tested, and confirmation of conformity with the product described in the application.
- The original analytical worksheets with calculations, the results of all tests performed, comments by the analyst(s), associated spectra, chromatograms, etc., and a comparison of the results obtained with the applicant's data and with the applicable specifications.
- An evaluation of each test performed by the applicant and the laboratory.
- A recommendation as to whether the methods are acceptable, acceptable only after specified changes have been made, or unacceptable.

If samples have not been collected in the course of a pre-approval inspection, the results of the analytical examination of the samples submitted by the applicant may nevertheless be used as supporting information.

The reserve samples, associated documentation and copies of laboratory reports should be stored in an orderly and retrievable way for a time period specified by national regulations. It is usually recommended that all material should be kept for a minimum of 3 years or for 1 year after the expiry date of the finished product.

## 8. Follow-up regulatory/administrative decisions

The inspectorate (inspection group of the drug regulatory authority) should recommend withholding approval when significant deviations from GMP requirements and other application commitments have occurred having an adverse effect on the product covered by the application. Examples of significant problems are:

- Misrepresentation of data or conditions relating to pre-approval batches.
- Pre-approval batches not manufactured in accordance with GMP.



- Inconsistencies and/or discrepancies raising significant questions concerning the validity of the records.

If applications are refused because of significant non-compliance with GMP, action must be taken to ensure that the necessary corrective measures are taken.

The drug regulatory authority is expected to advise the applicant that the inspectorate has recommended withholding approval of the application and give the reasons for this recommendation.

## References

1. Provisional guidelines on the inspection of pharmaceutical manufacturers. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report*. Geneva, World Health Organization, 1992, Annex 2 (WHO Technical Report Series, No. 823).
2. *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Vol. 2. Good manufacturing practices and inspection*. Geneva, World Health Organization, 1999.
3. Good manufacturing practices: guidelines on the validation of manufacturing processes. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report*. Geneva, World Health Organization, 1996, Annex 6 (WHO Technical Report Series, No. 863).
4. Good manufacturing practices: supplementary guidelines for the manufacture of investigational pharmaceutical products for clinical trials in humans. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report*. Geneva, World Health Organization, 1996, Annex 7 (WHO Technical Report Series, No. 863).

## Inspection of pharmaceutical manufacturers<sup>1</sup>

These guidelines are intended to promote harmonization of pharmaceutical inspection practices among WHO Member States. They are directed to government inspectors—particularly those operating within small national regulatory authorities (1)—to assist them in assessing manufacturers' compliance with good manufacturing practices (GMP) (2). They will also be of value to manufacturers themselves when engaged in self-inspection or audit.

They cover inspection of the production and control of final dosage forms of pharmaceutical products destined for human and veterinary use and of drug substances (active pharmaceutical ingredients or bulk drug substances) employed in their manufacture. Within the national context their scope may need to be

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<sup>1</sup> Provisional guidelines on the inspection of pharmaceutical manufacturers. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report*. Geneva, World Health Organization, 1992, Annex 2 (WHO Technical Report Series, No. 823).



extended since similar regulations are often enforced to control pharmaceutical and biological products, medical devices, diagnostic products, foods, and food additives. In all cases the same fundamental principles apply.

Inspection and licensing of pharmaceutical manufacturing facilities on the basis of compliance with GMP are a vital element of drug control. They are also pivotal to the operation of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (3), which requires an attestation by the competent regulatory authority in the exporting country that a given product is manufactured in premises and using operating practices that conform with GMP.

The guidelines also have relevance in various other contexts, including:

- self-inspection or internal audit of a factory or a part of it carried out by personnel of the company;
- inspection by an independent person or group of persons as a review of the quality system of a company in compliance with the standards issued by the International Organization for Standardization (ISO 9000–9004 (4)) or the British Standards Institution (BS 5750 (5)) or with other equivalent national standards;
- audit of a manufacturer or supplier by authorized agents of the customer.

The government inspectorate represents the enforcement arm of the national drug regulatory authority. Its function is to ensure adherence by manufacturers to all licensing provisions and specifically to GMP. The objectives are to control and enforce general standards of production and to provide authorization for the manufacture of specific pharmaceutical products. The first objective involves a sequential examination of production and control activities on the basis of the GMP guidelines issued by WHO or of nationally determined requirements. The second requires verification that production and quality control procedures employed in the manufacture of specific products are performed correctly and that they accord with data supplied in the relevant licensing applications.

Inspection will, of course, depend on national legislation and regulations and/or the resources available.

## The role of the inspector

Inspectors should have previous training and practical experience in the manufacture and/or quality control of pharmaceutical products. Graduate pharmacists, chemists, or scientists with an industrial background in pharmaceutical production would qualify for consideration.

In-post training should include an element of apprenticeship gained by accompanying experienced inspectors on site visits as well as participation in courses and seminars on relevant subjects including modern pharmaceutical technology, microbiology, and the statistical aspects of quality control.



The primary responsibility of an inspector is to present a detailed factual report on standards of manufacture and control applied to specific products. However, inspection should not be limited to compilation of an inventory of faults, irregularities, and discrepancies. Provided it is in keeping with national policy and does not breach understandings regarding confidentiality of information having commercial value, advice may be offered on how production and control procedures can be usefully upgraded. An inspector should always be expected, for example, to offer advice on how to improve an in-process test procedure or to offer other assistance which, in his or her opinion, serves the public interest. An inspection should be regarded as an opportunity to assist and motivate a manufacturer to comply with GMP and to correct any specific deficiencies.

## The inspection process

The planning, organization, method of work, and format of the resultant report should always be determined by the precise objective of the inspection. Inspections vary in nature according to the objective:

### Routine inspection

This is a full inspection of all applicable components of GMP and licensing provisions. It may be indicated when the manufacturer:

- is newly established;
- requests renewal of a licence to operate;
- has introduced new product lines or new products, or has made significant modifications to manufacturing methods or processes, or has made changes in key personnel, premises, equipment, etc.;
- has a history of non-compliance with GMP;
- has not been inspected during the last 3–5 years.

### Concise inspection

Manufacturers with a consistent record of compliance with GMP through previous routine inspections are eligible for concise inspection. The focus of a concise inspection is on a limited number of GMP requirements selected as indicators of overall GMP performance, plus the identification of any significant changes that could have been introduced since the last inspection. Collectively, the information obtained will indicate the overall attitude of the firm towards GMP. Evidence of unsatisfactory GMP performance observed during a concise inspection should trigger a more comprehensive inspection.



### Follow-up inspection (reassessment or reinspection)

Follow-up visits are made to monitor the result of corrective actions. They are normally carried out from 6 weeks to 6 months after the initial inspection, depending on the nature of the defects and the work to be undertaken. They are limited to specific GMP requirements that have not been observed or that have been inadequately implemented.

### Special inspection

Special visits may be necessary to undertake spot checks following complaints or recalls related to suspected quality defects in products. Reports of adverse drug reactions may also indicate that all is not well. Such inspections may be focused on one product, a group of related products, or specific operations such as mixing, sterilization, or labelling.

Special visits may also be made to establish how a specific product is manufactured as a prerequisite for marketing approval or issuance of an export certificate.

A further reason for special visits is to gather specific information on—or to investigate—specific operations and to advise the manufacturer of regulatory requirements.

### Quality systems review

A quality systems review is a relatively new concept. Its purpose is to describe a quality assurance system that has been shown to operate satisfactorily. It entails a description of the quality system and the standards to be observed, normally in a manual containing a statement of the manufacturer's policy on quality assurance. It should also define the management structure needed to implement the policy, along with the procedures in each management area needed to ensure that adequate quality standards are set for the product, manufacturing processes are correctly defined, records are kept, and quality control and other quality assurance activities are carried out.

### Frequency and duration of inspections

The frequency and duration of visits should be determined by the type of inspection required as well as by the workload and number of inspectors. New manufacturing establishments must be inspected before they are licensed, and new facilities must be inspected before production is started.

For all companies, inspections should be carried out on a regular schedule, ideally annually.

For large companies marketing a wide range of products, the inspection of the site may be split up into several visits over a longer period, e.g., 5 years



where this is the period of validity of the manufacturing licence or the GMP certificates.

The length of a given inspection is determined by the size of the company and the purpose of the visit. It can extend from a few days to 2 weeks or more. The time taken also depends on the number of inspectors assigned to the visit. In many countries, visits are made by one (or more) inspectors, sometimes accompanied by a specialist when production of biologicals, sterile production areas, or other special facilities are to be examined.

### Preparing for the inspection

Drug inspection begins at the desk of the inspector. A review should be made of the documents relating to the company to be visited, available from the drug regulatory authority. These may include the manufacturing licence, the marketing authorization dossiers for leading products, reports of adverse drug reactions, complaints and recall records, the results of regulatory (surveillance) testing, and the previous inspection reports.

Company documents, including the annual report for the shareholders, the complaints file, and self-inspection/internal audit reports, are valuable sources of information. The last of these, depending on national legislation, may be withheld from the inspector. In some countries, a compromise is reached, the company presenting the internal audit reports to the inspector for general information after the latter's own report has been finalized. In any case, it should be possible to verify the frequency of self-inspections, and to which parts of the plant they have been applied.

### Conduct

Announced inspections cover regular visits to evaluate new plants and new production lines and to decide on the renewal of a licence.

Unannounced inspections are necessary for concise, follow-up, and special visits.

In certain countries regular inspections are unannounced as a matter of policy.

The visit usually begins with a meeting between the inspector(s), representatives of the company or plant management, and those responsible for the products or areas to be inspected. Credentials should be presented, letters of authority inspected, and an explanation given of why the inspection is being carried out.

It is advantageous for the company to appoint at least one "escort" who is directly involved in the preparation of the products that are the object of the inspection. Escorts should be chosen who are generally familiar with the quality systems of the company and who are involved in the self-inspection programme.



## QUALITY ASSURANCE OF PHARMACEUTICALS

The meeting may be followed by a perusal of the company's documents by the inspector or by a walk-through visit, or both. This will permit the inspector to finalize the plan for the inspection. It is recommended that the inspector both develops and follows this plan independently, rather than accepting guidance from company management. Some basic rules for conducting the inspection are as follows:

- Inspection should follow the original plan as far as possible; items that are specific to certain areas of the facility, such as in-process testing and working documents, may need to be checked at the point of operation. Care should be taken to cover activities such as water production, sample storage, and validation.
- It is advisable to follow production flow from reception of the starting materials to the shipment of the finished products. The frequency of recalls and return of goods should be carefully noted.
- Documents such as master formulae, test specifications, standard operating procedures, and batch records (including protocols of analyses, etc. and documents relating to the control of printed materials and labelling operations) require close verification.

Without prejudice to the need to verify documentation, it is essential that the inspection be based largely on observation and cover the total working hours of the manufacturer. It is recommended that the inspector start the plant tour as soon as possible after arrival.

Inspectors can profitably use a short checklist to ensure that all areas of operations have been investigated. A very detailed checklist developed from GMP guidelines is of use specifically for the training of inspectors. Experience has shown that rigid adherence to a too-detailed checklist can lead to possible overlooking of vulnerable areas of a quality assurance system specific to the company/plant under investigation. For an experienced inspector, knowledge of the manufacturer's weak points allied with intuition may serve better than a checklist. Different checklists may be found in the recommended publications and documents listed in Appendix 1.

*Stability-testing programme.* The inspector should be satisfied that there exists a documented ongoing programme specifying the regular withdrawal of samples of all products from the production line for stability testing. The testing schedule for stored samples should employ appropriate conditions of temperature and light stress, and suitable stability-indicating analytical methods that yield conclusions consistent with claimed shelf-life. The systems should permit re-evaluation of product stability following any changes in the manufacturing process or formula.

Significant changes in facilities, equipment, products, and senior personnel since the last inspection should be noted. The principle here is that changes represent possible areas of weakness or causes of non-compliance with GMP. For example, new equipment may require changes to be made in procedures; new





product lines may require new product master files; and departures of senior personnel such as the quality control manager may result in behavioural or procedural changes.

Occasionally, an inspector may require access to other premises, documents, or information on the company. Ideally, the inspector's authority should be determined by legislation, but in the absence of clear legal or regulatory provisions, it is suggested that the GMP code is used as a guide and the inspector should have the right to verify compliance with every requirement listed in the code.

The inspector should not be concerned about information not covered by GMP—e.g., finance and personnel—where this does not infringe on the company's responsibilities or staff education and training.

Photographs or videos taken during the visit may be excellent illustrative material for the report. National legislation should stipulate that the inspector has the right to take visual records during the inspection to document the production premises or laboratories.

In many cases, an aerial photograph of the manufacturing site, possibly with surrounding grounds, may be obtained from the company together with other relevant materials for inclusion in the report.

*Collecting samples.* It is normal practice during the visit for the inspector to take samples for testing by the official quality control laboratory. Samples are usually taken from released products (e.g., from the finished-goods warehouse) but may also be taken from stocks of raw materials or in-process material. In order to protect sample integrity, any protocol meant for enforcement or legal purposes should set out the procedures for sample collection, analysis, and documentation. The following should be stated:

- name(s) of the sampled product(s), batch number(s), date, source, number of samples, and remarks on type of packaging and storage conditions;
- circumstances of sampling, e.g., suspected quality defects, routine surveillance, verification of compliance with GMP;
- instructions for the placing of seals on containers of sample materials;
- written confirmation of the receipt of the samples by the inspector (possibly together with the manufacturer's certificates of analysis and any other supporting documents).

The manufacturer, represented by the company escort, should be encouraged to take duplicate samples from the same batch(es), for "in-house" testing if a problem is later identified.

Before the inspector leaves the premises after the inspection, a final discussion with company management is recommended. If possible, the inspector should list any unsatisfactory findings and outline any irregularities or other observations to which management may wish to respond.



## Report

It is recommended that reports be divided into four parts: general information on the company or manufacturing facility, description of the inspection, observations, and conclusions. Annexes may contain supporting information (a list of products manufactured, an organization chart, the annual company report, photographs, etc.). The third and fourth parts may be combined. Appendix 2, which is an extract from a document prepared for the Pharmaceutical Inspection Convention, provides an example of the form and content of the inspector's report.

In order to save the inspector's time, the first part of the report containing basic data may be supplied by the company beforehand, provided that this fact is clearly stated in the report and the information supplied is verified by the inspector during the visit. An example of items that should be considered for inclusion is given in Appendix 2, section C "Site master file".

The second part should describe the complete progress of the inspection step by step, documenting which parts of the factory, warehouses, laboratories, records, documents, etc. were inspected.

The third part is devoted to observations. Changes, improvements, and examples of deterioration since the previous inspection should be noted by the inspector.

Positive observations should take the form of a description of the processes that the firm is carrying out particularly well and that may be considered examples of particularly good manufacturing practice.

Negative observations (non-compliance with GMP requirements) should distinguish between whether the defect lies in the system itself or in a failure to comply with the system. For instance, when cleaning is found to be suboptimal, it is important to know whether the standard operating procedures are inadequate or lacking, or whether adequate written procedures exist but are not being followed by personnel.

In the final part of the report, the inspector should summarize deficiencies, unsatisfactory practices, etc. (listed in decreasing order of importance), suggest corrective actions, and make recommendations. This part, together with the third part, should be discussed with the company management and responsible authorized persons at the end of the inspection.

A copy of the complete written report, after supervisory approval, should be provided to the company management with a covering letter. The corrective actions to be taken, together with a time limit for their execution, should also be presented to the management of the company.

Inspection reports may be treated as confidential documents depending on national legislation. Under certain international agreements, reports may be exchanged between drug regulatory authorities.



## Regulatory actions

Depending on national legislation, regulatory authorities may take action to correct unsatisfactory practices and prevent the distribution of products with suspected quality defects or manufactured under conditions that do not comply with GMP requirements. In extreme cases, the closing down of operations may be required. In practice, these measures are used only in exceptional cases constituting a hazard to health.

In many countries, the drug regulatory authority has the legal power to suspend or revoke the marketing authorization for a product when the manufacturer does not comply with GMP. In addition, manufacturing or marketing authorizations (licences), the reregistration of products, and the issue of a variation licence or a GMP certificate may be delayed until appropriate measures have been taken by the company, and possibly have been confirmed by reinspection. As a rule, the manufacturer concerned has the right to appeal.

## References

1. Guiding principles for small national drug regulatory authorities. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-first report*. Geneva, World Health Organization, 1990: 64–79 (WHO Technical Report Series, No. 790).
2. Good manufacturing practices for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report*. Geneva, World Health Organization, 1992: 14–79 (WHO Technical Report Series, No. 823).
3. WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-first report*. Geneva, World Health Organization, 1990: 57–63 (WHO Technical Report Series, No. 790).
4. *International Standards: Quality management and quality assurance standards—Guidelines for selection and use (ISO 9000), Quality systems—Model for quality assurance in design/development, production, installation and servicing (ISO 9001); Quality systems—Model for quality assurance in production and installation (ISO 9002); Quality systems—Model for quality assurance in final inspection and test (ISO 9003); Quality management and quality system elements—Guidelines (ISO 9004)*. Geneva, International Organization for Standardization. 1987 (rev. 1990).
5. *Quality systems. Part 2. Specification for manufacture and installation (BS 5750: Part 2)*. London, British Standards Institution, 1979.



## Appendix 1. Recommended publications and documents

*ASEAN manual for inspection of GMP*. Association of South East Asian Nations, 1988.

Drug manufacturer's self-inspection manual as to conformity with GMP requirements. In: *GMP regulations of Japan*, 3rd ed. Tokyo, Ministry of Health and Welfare, 1988: 101–195.

*Good drug manufacturing practices (GMP), audit check-list*. Government of Brazil, Ministry of Health, 1983.

Grundregeln für die Herstellung von Wirkstoffen und die Sicherung ihrer Qualität; Fragebogen zu den Grundregeln für die Herstellung von Wirkstoffen und die Sicherung ihrer Qualität [Basic rules for the production of active ingredients and their quality assurance; audit checklist to the basic rules for the production of active ingredients and their quality assurance]. *Pharmazeutische Industrie*, 1981, **43**: 537–542 (republished in: **Oeser W, Sander A**. *Pharma-Betriebsverordnung, Kommentar [GMP comments]*. Stuttgart, Wissenschaftliche Verlagsgesellschaft, 1988).

*Guide to inspection of bulk pharmaceutical chemical manufacturing*. Food and Drug Administration, US Department of Health and Human Services, Public Health Service, 1987.

**Steinborn L**. *Quality assurance manual for the pharmaceutical and medical device industries*. Buffalo Grove, IL, Interpharm Press, 1986.

## Appendix 2. Form and content of the inspector's report<sup>1</sup>

### A. Inspector's information

1. Date of inspection(s) on which the information is based and name(s) of inspector(s).
2. Brief report of inspection activities undertaken.
3. Samples taken and results obtained.
4. Assessment of the site master file (see section C).
5. GMP-related recalls from the market of any product in the last two years.

### B. Summary and conclusions

1. The inspector's general impression of the firm and his or her assessment of the acceptability of its GMP status for the range of products concerned.

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<sup>1</sup> Extracted (with permission and minor changes) from an unpublished document (PH 6/91) prepared for the Pharmaceutical Inspection Convention, November 1991.



2. Failures to comply with the PIC Guide to Good Manufacturing Practice (in order of importance) and with the time limits set for them to be corrected by the manufacturer.

### C. Site master file

A site master file is a document prepared by the manufacturer containing specific and factual GMP information about the production and/or control of pharmaceutical manufacturing operations carried out at the named site and any closely integrated operations at adjacent and nearby buildings. If only part of a pharmaceutical operation is carried out on the site, the site master file need describe only those operations, e.g., analysis, packaging.

A site master file should be succinct and, as far as possible, not exceed 25 A4 pages.

#### **1. General information**

- 1.1 Brief information on the firm (including name and address), relation to other sites, and, in particular, any information relevant to understanding the manufacturing operations.
- 1.2 Pharmaceutical manufacturing activities as licensed by the national authority.
- 1.3 Any other manufacturing activities carried out on the site.
- 1.4 Name and exact address of the site, including telephone, fax, and 24-hour telephone numbers.
- 1.5 Type of products manufactured on the site, and information about any specifically toxic or hazardous substances handled, mentioning the way they are manufactured (in dedicated facilities or on a campaign basis).
- 1.6 Short description of the site (size, location, and immediate environment and other manufacturing activities on the site).
- 1.7 Number of employees engaged in production, quality control, storage, and distribution.
- 1.8 Use of outside scientific, analytical, or other technical assistance in relation to manufacture and analysis.
- 1.9 Short description of the quality management system of the firm responsible for manufacture.

#### **2. Personnel**

- 2.1 Organization chart showing the arrangements for quality assurance, including production and quality control.



## QUALITY ASSURANCE OF PHARMACEUTICALS

- 2.2 Qualifications, experience, and responsibilities of key personnel.
- 2.3 Outline of arrangements for basic and in-service training and how records are maintained.
- 2.4 Health requirements for personnel engaged in production.
- 2.5 Personnel hygiene requirements, including clothing.

### **3. Premises and equipment**

#### Premises

- 3.1 Simple plan or description of manufacturing areas with indication of scale (architectural or engineering drawings not required).
- 3.2 Nature of construction and finishes.
- 3.3 Brief description of ventilation systems. More details should be given for critical areas with potential risks of airborne contamination (schematic drawings of the systems are desirable). Classification of the rooms used for the manufacture of sterile products should be mentioned.
- 3.4 Special areas for the handling of highly toxic, hazardous, and sensitizing materials.
- 3.5 Brief description of water systems (schematic drawings of the systems are desirable), including sanitation.
- 3.6 Description of planned preventive maintenance programmes for premises and of the recording system.

#### Equipment

- 3.7 Brief description of major equipment used in production and control laboratories (a list of equipment is not required).
- 3.8 Description of planned preventive maintenance programmes for equipment and of the recording system.
- 3.9 Qualification and calibration, including the recording system. Arrangements for computerized systems validation.

#### Sanitation

- 3.10 Availability of written specifications and procedures for cleaning manufacturing areas and equipment.



#### **4. Documentation**

4.1 Arrangements for the preparation, revision, and distribution of necessary documentation for manufacture.

4.2 Any other documentation related to product quality that is not mentioned elsewhere (e.g., microbiological controls on air and water).

#### **5. Production**

5.1 Brief description of production operations using, wherever possible, flow sheets and charts specifying important parameters.

5.2 Arrangements for the handling of starting materials, packaging materials, and bulk and finished products, including sampling, quarantine, release, and storage.

5.3 Arrangements for the handling of rejected materials and products.

5.4 Brief description of general policy for process validation.

#### **6. Quality control**

6.1 Description of the quality control system and of the activities of the quality control department. Procedures for the release of finished products.

#### **7. Contract manufacture and analysis**

7.1 Description of the way in which the GMP compliance of the contract acceptor is assessed.

#### **8. Distribution, complaints, and product recall**

8.1 Arrangements and recording system for distribution.

8.2 Arrangements for the handling of complaints and product recalls.

#### **9. Self-inspections**

9.1 Short description of the self-inspection system.

### Inspection of drug distribution channels<sup>1</sup>

Introductory note	158
General considerations	159

<sup>1</sup> Guidelines for inspection of drug distribution channels. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fifth report*. Geneva, World Health Organization, 1999, Annex 6 (WHO Technical Report Series, No. 885).



## QUALITY ASSURANCE OF PHARMACEUTICALS

Glossary	160
1. Drug inspectors	163
1.1 Qualifications	163
1.2 Organizational aspects	164
1.3 Methods of inspection	165
1.4 Reference/information sources	166
2. Inspection of establishments in the drug distribution chain	167
2.1 Broad objectives	167
2.2 Establishments	167
2.3 Inspections	167
2.4 Special categories of drugs	167
References	168
Selected further reading	168
Appendix 1	
Checklist for inspection and the preparation of a report	169
Appendix 2	
Guidance on sampling	173
Appendix 3	
Guidance for inspection when pharmaceutical products are suspected to be counterfeit, spurious or substandard	174
Appendix 4	
Sample receipt form	175

### Introductory note

The quality assurance of drugs at the level of the manufacturer is outlined in the guidelines on good manufacturing practices for pharmaceutical products (GMP) published by WHO (1). Compliance with these guidelines will ensure that products released for distribution are of the appropriate quality. However, if this is to be realized in practice, it is essential that an established drug regulatory authority exists in a Member State, which complies at least with the “Guiding principles for small national drug regulatory authorities” (2).

In addition, the holder of a marketing authorization for a pharmaceutical product, or alternatively the (legal) person responsible for the initial marketing of a product, who ideally should be a pharmacist or a pharmaceutical company authorized to practise in the Member State, should ensure that the product is only released for distribution after it has been established that it conforms with the product specification lodged with the drug regulatory authority.

This level of quality should be maintained throughout the pharmaceutical supply system or distribution network. Basic principles of GMP are applicable to wholesale operations and (to some extent) to retail outlets. These principles may be summarized as follows:





- only authorized products are distributed;
- a quality system is in place which includes quality policy, quality management, appropriate analytical controls, self-inspection;
- personnel are quality-conscious, adequately trained and motivated;
- premises and equipment are suitable for their intended use, and kept in a good sanitary condition;
- all products are received, stored and handled appropriately (protected against contamination, cross-contamination, mix-ups, environmental factors such as heat, severe cold, moisture, light);
- all drug-related operations are performed in accordance with written procedures, are properly supervised and adequately documented; documentation ensures complete traceability of receipt of all materials, quality testing processes (if any) and shipping;
- adequate provisions exist to handle complaints, recalls, and returned goods.

At the same time, many provisions of the GMP guidelines published by WHO are clearly not addressed to wholesalers and retail pharmacies where specific rules and requirements apply. These rules are determined partly by pharmaceutical science and common sense, and partly by national (regional) regulations and standards. In this context reference is made particularly to the guidelines entitled “Good pharmacy practice in community and hospital pharmacy settings” (3). It follows then that the “Provisional guidelines on the inspection of pharmaceutical manufacturers” (4), which are directed to government GMP inspectors, are not adequate to cover inspection in the distribution system. The present document addresses this specific issue.

These guidelines are intended for use by pharmaceutical inspectors in national drug regulatory authorities. They are therefore presented in a format that will allow for easy reference in the field. They should, however, be adapted by national drug regulatory authorities to suit their national legal requirements and available resources.

This document discusses the “simplified” situation when there is a single authority, the drug regulatory authority, where all kinds of drug inspections are located, ranging from those of drug manufacture to the inspections of pharmacies. In reality, these tasks, requiring different inspection skills are usually distributed among different (national and local) authorities.

## General considerations

A comprehensive system to assure the safety, efficacy and quality of pharmaceutical products at a national level has the following elements:

- Legal: drug legislation
- Administrative:
  - drug regulatory authority with functions of product registration, licensing of manufacturers, importers and distributors (wholesale, retail



## QUALITY ASSURANCE OF PHARMACEUTICALS

- and for institutional supply), inspection and independent testing of samples
- enforcement
- Technical:
  - regulations
  - standards and norms
  - guidelines
  - independent quality control laboratory(ies)

This document focuses on one element—inspection—and in particular on inspection in the pharmaceutical supply system.

The usefulness of drugs in the treatment of ailments, diseases and disorders is well recognized and appreciated. It is also recognized that the inappropriate use of drugs can produce severe toxic effects, some of which may be fatal. National drug laws have therefore been introduced to reduce risks associated with the use, misuse and abuse of pharmaceutical preparations.

Drugs differ in the severity of their side-effects and toxicity and these differences are taken into consideration in the classification of drugs in national drug laws. Drugs may be classified into four types as follows: over-the-counter drugs, pharmacy-only drugs, prescription-only drugs and prohibited drugs.

The distribution, supply, import, export, sale, storage, advertisement and dispensing of drugs are normally regulated by national drug laws, which provide for a system of licences to be issued by a drug regulatory authority for such drug-related activities. The drug laws may identify a ministry/department/agency that would function as the drug regulatory authority as well as provide for the enforcement of the drug laws, using a system of inspections organized through an inspectorate(s).

The inspectorate advises on whether applicants and premises should be issued licences to engage in drug-related activities. The inspectorate ensures that counterfeit, spurious and substandard pharmaceutical products are not found in the national pharmaceutical supply system or outside it, and that licensed premises and authorized persons adhere to existing laws and regulations. To do this, the inspectorate gathers information on the working of the drug laws by liaising with other law enforcement agencies and health institutions, including health-care professional associations.

## Glossary

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

### *batch*

A defined quantity of any drug product processed in a single process or series of processes such that it can reasonably be expected to be uniform in character and quality.



*batch number*<sup>1</sup>

A distinctive combination of numbers and/or letters which specifically identifies a batch on the labels, the batch records, the certificate of analysis, etc.

*controlled drugs*

Narcotic drugs and psychotropic substances regulated by provisions of national drug laws.

*counterfeit pharmaceutical product*

A pharmaceutical product which is deliberately and fraudulently mislabelled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients, with the wrong ingredients, without active ingredients, with an insufficient quantity of active ingredient or with fake packaging.

*drug (pharmaceutical product)*

Any substance or mixture of substances that is manufactured for sale or distribution, sold, supplied, offered for sale or presented for use in:

- (i) the treatment, mitigation, cure, prevention or diagnosis of disease, an abnormal physical state or the symptoms thereof and abnormal physiological conditions in human or animal; or
- (ii) the restoration, correction or modification of organic functions in human or animal.

*finished pharmaceutical product*

A pharmaceutical product that has undergone all stages of production and quality control, including being packaged in its final container and labelled.

*good manufacturing practice*<sup>1</sup>

Good manufacturing practice is that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization.

*good pharmacy practice*

The practice of pharmacy aimed at providing and promoting the best use of drugs and other health care services and products, by patients and members of the public. It requires that the welfare of the patient is the pharmacist's prime concern at all times.

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<sup>1</sup> As defined in "Good manufacturing practices for pharmaceutical products" (1).



## QUALITY ASSURANCE OF PHARMACEUTICALS

### *over-the-counter drugs*

These are drugs that can be sold from licensed dealers without professional supervision and without prescriptions. These drugs are suitable for self-medication for minor diseases and symptoms.

### *pharmacist*

A pharmacist is a holder of a degree or diploma in pharmacy from a recognized higher institution of learning and is registered or licensed to practise pharmacy.

### *pharmacy-only drugs*

These are drugs authorized to be sold only in licensed pharmacies under the supervision of licensed and registered pharmacists; they may be sold without a prescription.

### *poison*

A preparation or substance defined by a national drug law as a poison.

### *prescription-only drugs*

These are drugs supplied only in licensed pharmacies on the presentation of signed prescriptions issued by a licensed and registered medical practitioner, licensed and/or registered dentist (for dental treatment only), and/or licensed and/or registered veterinarian (for animal treatment only), and the supply and dispensing of these drugs must be carried out by a pharmacist or under the supervision of a pharmacist. Prescription drugs are further subdivided into controlled drugs (narcotic drugs and psychotropic substances) and non-controlled drugs.

### *product recall*

Product recall is a process for withdrawing or removing a pharmaceutical product from the pharmaceutical distribution chain because of defects in the product or complaints of serious adverse reactions to the product. The recall might be initiated by the manufacturer/importer/distributor or a responsible agency.

### *prohibited drugs*

These are drugs with toxicity or side-effects that outweigh their therapeutic usefulness, so that public health and welfare are protected by prohibiting their production, manufacture, export, import, trade, distribution, supply, possession or use, except in amounts required for medical and scientific research. Prohibited drugs are normally determined by the national or supranational registration/licensing authority.



*quality assurance*<sup>1</sup>

Quality assurance is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use.

*quality control*

Quality control covers all measures taken, including the setting of specifications, sampling, testing and analytical clearance, to ensure that raw materials, intermediates, packaging materials and finished pharmaceutical products conform with established specifications for identity, strength, purity and other characteristics.

*unauthorized market (in some countries called parallel market)*

The unauthorized market consists of wholesale establishments and retail outlets distributing or selling drugs without authorization from a competent authority.

## 1. Drug inspectors

### **1.1 Qualifications**

Inspectors should normally be pharmacists who have working experience in community and/or hospital pharmacy. Where persons other than pharmacists are employed as drug inspectors, they should be adequately experienced in drug control affairs and suitably trained in inspectorate functions. The possibility of having part-time inspectors with specialist knowledge as part of inspection teams should also be considered.

The inspector should possess the following attributes:

- good knowledge of pharmacy, drugs, and poisons
- good knowledge of the laws and regulations to be enforced
- good command of technical terms and excellent communication skills
- awareness of the probable methods of using forged or false documents for transactions in pharmaceutical preparations and skill in determining the genuineness of documents presented for examination
- maturity, honesty and integrity
- responsible conduct which commands respect
- willingness to accept challenges
- ability to organize their own work with minimum supervision
- ability to assess facts quickly and take rational and sound decisions without delay

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<sup>1</sup> As defined in "Good manufacturing practices for pharmaceutical products" (1).



## QUALITY ASSURANCE OF PHARMACEUTICALS

- ability to assess character and honesty of persons being interviewed
- good public relations image with key personnel/pharmacists in charge of premises while remaining firm, fair and resolute
- ability to hold discussions with company management at the completion of inspection
- ability to motivate others
- commitment to hard work and long hours
- ethical approach to any potential conflict of interest.

### **1.2 Organizational aspects**

Inspectors should be embedded in an organization, usually called an inspectorate, which ensures the following aspects:

- A job description which describes the duties of the inspector.
- Proper reporting: inspectors should report either to the drug regulatory authority or to the pharmaceutical department (chief pharmacist) of the ministry of health.
- Uniformity of approach:
  - (a) Regular meetings of inspectors, in which experiences on the job are exchanged, will help promote a uniform approach to inspection as well as enhance the performance of the inspectors.
  - (b) Inspectors should work according to a work plan and to Standard Operating Procedures (SOPs).
  - (c) Inspection reports should preferably be in three or four parts:
    - (i) date of inspection and general information on the establishment inspected,
    - (ii) description of the inspection activities undertaken, including analytical data of samples taken,
    - (iii) observations and recommendations,
    - (iv) conclusions.
  - (d) Inspectors should be encouraged to submit weekly reports of work to headquarters.
- Total coverage of the country. This can be achieved by:
  - (a) dividing the country into defined areas for the purpose of inspection and placing an inspector in charge of a defined area for the purpose of inspecting wholesale, community and hospital pharmacies, and clinics,
  - (b) inspection of ports and border posts in a defined area.
- Total coverage of the field. The inspector will be expected to inspect establishments such as:
  - (a) pharmaceutical manufacturers in respect of drug distribution,
  - (b) pharmaceutical importers/exporters,
  - (c) pharmaceutical wholesalers and retailers,



- (d) hospital pharmacies/clinics,
- (e) ports and international border posts,
- (f) drug warehouses, stores and unauthorized markets.

(Note: The existence of unauthorized markets for the distribution of drugs poses considerable health hazards. The inspectors should, with the assistance of task forces if necessary, investigate the extent of the unauthorized market, the types of drugs distributed and supplied, and the sources of the drugs. Where possible, unauthorized markets for drugs should be prohibited through effective inspectorate activities. Inspectors should also investigate the sources of supply of suspect counterfeit or substandard pharmaceutical products.)

- Cooperation with other agencies. The inspector will be expected to interact and cooperate with other interested parties such as:
  - (a) industrial, community and hospital pharmacists,
  - (b) management and supervisory staff of pharmaceutical establishments and hospitals,
  - (c) medical practitioners, dentists, veterinarians, nurses and midwives and other health workers,
  - (d) public analysts,
  - (e) ministry of justice officials and court officials,
  - (f) drug law enforcement officers including the police and customs,
  - (g) officers of port authorities, clearing agents at the ports, importers and exporters,
  - (h) members of the public,
  - (i) staff of faculties of medicine/pharmacy,
  - (j) foreign drug regulatory authorities.
- Independence. Inspectors should, for example, have the use of official vehicles.
- Adherence to a code of inspection.

### **1.3 Methods of inspection**

The inspector uses different methods to check compliance with the national, supranational or international drug laws and regulations. Among these methods are:

- *Comprehensive/routine inspection.* This form of inspection is generally reserved for a new pharmaceutical establishment, when an establishment is applying for permit to extend its scope of operations beyond that for which it was originally licensed, has made important changes in key personnel or is changing premises, has not been inspected for a long time (3–5 years), or when there is information (even of an informal nature) of serious lapses. Where the inspection is for a new establishment or for extension of scope of operation or because of changes in key personnel, the inspection should be announced.



## QUALITY ASSURANCE OF PHARMACEUTICALS

- *Concise inspection.* This is reserved for establishments that have previously been inspected with a view to assessing standards of good pharmacy practice. The outcome of the inspection will help in the proper assessment of the establishment. The inspection may be unannounced.
- *Follow-up inspection.* This is normally carried out to ensure that corrective measures have been undertaken following advice and notice given during a previous inspection. Where a time limit was given for applying the corrective measures, the inspection may be unannounced.
- *Special inspection.* This is undertaken to deal with specific complaints received about lapses or non-compliance with standards of professional practice. The inspection should preferably be unannounced.
- *Investigative inspection.* This type of inspection is used to assess the performance of a new establishment whose scope of operation was previously unknown.

Any of these methods may be applied with or without prior announcement. Normally inspections should be announced but it serves a useful purpose to undertake some unannounced inspections. Follow-up, special and investigative inspections should preferably be unannounced.

Inspections should be held regularly. Premises should be inspected at least once every 12–18 months. Where contravention is often noticed, the inspection should be more frequent (e.g. every six months). For premises with a good record, less frequent inspections may be needed.

### **1.4 Reference/information sources**

The reference/information sources of an inspector should include:

- Existing national and international drug laws and regulations, covering such aspects as:
  - licensing
  - GMP
  - good distribution practice
  - good pharmacy practice
  - promotion of pharmaceutical products
  - controlled drugs
  - counterfeit, spurious or substandard pharmaceutical products.
- Codes of inspection (national and regional), where in existence.
- Codes of professional ethics.
- Health consequences of drug abuse and misuse.
- Available data on imports/exports/prohibited drugs.





## 2. Inspection of establishments in the drug distribution chain

### **2.1 Broad objectives**

The welfare of patients and other members of the public is of prime concern in the distribution chain of drugs, either manufactured within the country or imported. Inspections of establishments are therefore undertaken to ensure:

- Protection of patients and members of the public from malpractice by distributors and suppliers of drugs.
- Adherence to the drug laws and regulations governing compounding, distribution, importation, export and storage of drugs.
- High ethical and professional standards of pharmaceutical practice.

### **2.2 Establishments**

In the drug distribution chain several kinds of establishments can be distinguished:

- production sites
- storage or warehouse facilities
- establishments for the supply, sale, dispensing and distribution of drugs, such as pharmacies, hospitals, clinics, ports and stores.

### **2.3 Inspections**

When inspecting these establishments the inspector uses the appropriate references. The method of inspection should be laid down in a SOP which also contains the requirements for a specific type of establishment. The inspection SOP may be in the format of a checklist (see Appendix 1 for an example applicable to most drug distribution establishments). When sampling is part of the inspection procedure, the SOP should contain detailed guidance for the inspector; an example of this guidance is to be found in Appendix 2.

### **2.4 Special categories of drugs**

When special categories of drugs are present the inspector may require a modified SOP. This situation is likely to occur with controlled drugs, pharmaceutical products moving in international commerce, or with counterfeit, spurious or substandard pharmaceutical products. For this last category an example of extra guidance is given in Appendix 3.



## References

1. Good manufacturing practices for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report*. Geneva, World Health Organization, 1992, Annex 1 (WHO Technical Report Series, No. 823).
2. Guiding principles for small national drug regulatory authorities. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-first report*. Geneva, World Health Organization, 1990, Annex 6 (WHO Technical Report Series No. 790).
3. Good pharmacy practice in community and hospital pharmacy settings. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fifth report*. Geneva, World Health Organization, 1998, Annex 7 (WHO Technical Report Series, No. 885).
4. Provisional guidelines on the inspection of pharmaceutical manufacturers. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report*. Geneva, World Health Organization, 1992, Annex 2 (WHO Technical Report Series, No. 823).

## Selected further reading

*ASEAN good manufacturing practices guidelines*, 2nd ed. Jakarta, Technical Cooperation on Pharmaceuticals, 1988.

*Basic tests for pharmaceutical substances*. Geneva, World Health Organization, 1986.

*Basic tests for pharmaceutical dosage forms*. Geneva, World Health Organization, 1991.

*Bulk pharmaceutical chemicals*. London, Institute of Quality Assurance, 1992 (Pharmaceutical Quality Group Monograph).

Code of ethics. *Pharmaceutical journal*, 1992, **248**:545–556.

*Convention on Psychotropic Substances, 1971*. New York, United Nations, 1977.

*Ethical criteria for medicinal drug promotion*. Geneva, World Health Organization, 1988.

Hayes P, Kayne S, Martin T, McMurdo A. Use of professional self audit in pharmacy practice. *Pharmaceutical journal*, 1992, **249**:650–652.

*International nonproprietary names (INN) for pharmaceutical substances: Lists 1–73 of proposed INN and lists 1–35 of recommended INN; cumulative list no. 9*. Geneva, World Health Organization, 1996.

Sampling procedures for industrially manufactured pharmaceuticals. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-first report*. Geneva, World Health Organization, 1990, Annex 2 (WHO Technical Report Series, No. 790).



*Single Convention on Narcotic Drugs, 1961, as amended by the 1972 Protocol.* New York, United Nations, 1977.

Statutory Committee: professional conduct. *Pharmaceutical journal*, 1969, **203**:472.

Statutory Committee: three names to be removed from register. *Pharmaceutical journal*, 1973, **210**:212.

Turner JL. The implementation of European Community directives concerning GMP. *Drug information journal*, 1991, **25**:537–544.

*United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances, 1988.* New York, United Nations, 1991.

Wingfield J. Misconduct and the pharmacist. *Pharmaceutical journal*, 1990, **245**:531–533.

## **Appendix 1**

### **Checklist for inspection and the preparation of a report**

Inspection applicable to all drug distribution establishments

#### **1. General information**

- (a) name of establishment inspected
- (b) date of inspection
- (c) name(s) of the inspector(s)
- (d) date of last inspection.

#### **2. Type of inspection**

Comprehensive, concise, follow-up, special, investigative, announced, unannounced.

#### **3. Licensing**

- (a) licensing of premises
- (b) person with supervisory role in establishments handling prescriptions and pharmacy sale-only drugs (is normally a registered pharmacist or a person so prescribed by national legislation)
- (c) personnel authorized to sell only over-the-counter drugs (licensed, where such licensing is required)
- (d) adherence to licensing provisions.



#### **4. Activities undertaken on premises**

Manufacturing, wholesale, importation, export, retail, hospital pharmacy, clinic, nursing and maternity homes.

#### **5. Adequacy and suitability of premises**

- (a) premises clean, tidy and in good state of repair
- (b) premises secure
- (c) floor durable and easily cleaned
- (d) premises constructed to prevent infestation by vermin and pests
- (e) clean shelves in retail pharmacy and premises for sale of over-the-counter drugs
- (f) changing rooms and toilet available
- (g) adequacy of lighting and ventilation
- (h) appropriate layout of premises.

#### **6. Warehouse/store**

- (a) adequacy and suitability of warehouse/store
- (b) warehouse/store clean and uncluttered
- (c) warehouse/store inaccessible to unauthorized persons
- (d) temperature and humidity control
- (e) enforcement of stock rotation
- (f) adequacy of shelving
- (g) existence of areas for returned drugs, recalled drugs, expired drugs, and drugs in quarantine
- (h) warehouse/store free from vermin and insects.

#### **7. Special storage**

- (a) availability of cold room storage or refrigerator for vaccines and biological products
- (b) suitability of the cold storage facilities
- (c) standard written procedure prepared by an appropriate national regulatory agency for the maintenance of cold chain
- (d) special storage area for controlled drugs and other prescription drugs
- (e) suitable and secure storage facility for controlled drugs and poisons.

#### **8. Record-keeping**

- (a) name and address of supplier of each drug product with date
- (b) name and address of purchaser of each drug product with date
- (c) supplier or purchaser licensed



- (d) retention of order forms, copy of delivery notes, stores receipt, and issue vouchers, and book of records (controlled drugs book/prescription drugs book) on the premises as provided for in the drug laws
- (e) accuracy of records kept.

**9. Conditions for sale and supply**

- (a) sale and supply of prescription and pharmacy sale-only drugs under the control of a registered pharmacist
- (b) sale and supply of prescription and pharmacy sale-only drugs effected from registered/licensed premises
- (c) sale of prescription drugs on the basis of valid prescription
- (d) sale and supply of over-the-counter drugs undertaken in registered premises under the supervision of a pharmacist or premises licensed for the purpose of sale and supply of over-the-counter drugs only, where such registration or licence is required by law.

**10. Diversion of controlled drugs**

Diversion of controlled drugs prevented by examining the records and by physical examination of stock.

**11. Returned and expired drugs**

Procedures in place for handling returned and time-expired drugs.

**12. Product recall**

Procedures in place for recall of drugs and handling recalled drugs.

**13. Product complaints**

Procedures in place for dealing with complaints about drugs.

**14. Promotional activities**

Assess promotional materials for compliance with drug laws.

**15. Personnel**

- (a) person responsible for supervising sale in a wholesale/retail pharmacy is a registered/licensed pharmacist
- (b) name of the pharmacist in continuous personal control noted
- (c) personnel wear clean protective clothing.



### **16. Labelling of drug products and package inserts**

Check adequacy of labelling of drug and information on package inserts.

### **17. Physical examination and sampling of drugs**

Conduct physical examination of drugs in stock and take samples of drugs for quality assessment.

### **18. Reference books**

Check existence of reference books on premises, where they are required.

Specific inspection applicable to individual establishments

### **19. Importer**

- (a) all drugs accompanied by import documents such as bill of lading, export authorization, product licence and batch certificate
- (b) controlled drugs also accompanied by export authorization certificate or export declaration, whichever is applicable
- (c) imported drugs are in original packs, except for drugs imported in bulk for repackaging and/or manufacturing drug formulations.

### **20. Retail and hospital pharmacy**

- (a) compounding of drugs carried out by or under the supervision of a pharmacist
- (b) quality of raw materials used in compounding complies with pharmacopoeial specifications
- (c) dispensing of prescription drugs carried out by or under the supervision of a pharmacist
- (d) entries of dispensed prescription drugs made in prescription book and for controlled drugs in controlled drugs book
- (e) prescriptions for prescription drugs retained on premises for periods provided in the drug laws
- (f) dispensed drugs labelled appropriately with name of drug, name of patient, name and address of pharmacy, clinic or hospital, instructions for using the drugs and, where appropriate, warning labels
- (g) counselling of patients on use of dispensed drugs
- (h) adequacy of containers for dispensed drugs
- (i) personnel observe high standard of personal hygiene and wear clean protective clothing
- (j) dispensing area clean, adequate and has necessary equipment
- (k) walls in dispensing area easily cleaned



- (l) quality of extemporaneous preparations
- (m) sources of drugs sold and supplied from the pharmacy
- (n) suitable cabinets for storage of controlled drugs and poisons.

### **21. Clinics, nursing and maternity homes**

- (a) sources of drugs used, supplied and administered
- (b) records of controlled drugs used, supplied and administered
- (c) storage facilities and security for controlled drugs.

### **22. Unauthorized markets**

- (a) investigate sources of drugs in the unauthorized market
- (b) sample drugs for quality assessment
- (c) seize drugs in the unauthorized market.

## **Appendix 2 Guidance on sampling**

This guidance is applicable to collecting samples of drugs to be tested by the official quality control laboratory. The collection may be aimed either at assessing the quality of products on the market, in which case adequate sampling plans should apply (see, for example, “Sampling procedures for industrially manufactured pharmaceuticals” (1, 2)), or at detecting substandard, spurious and counterfeit pharmaceutical products. In this case sampling shall be based on information and may involve confiscation of entire stocks to prevent further distribution. Compliance with legal procedures for sample collection, analysis and documentation is obligatory.

- (a) Check that the sample is properly labelled with the following:
  - (i) name of sampled pharmaceutical preparation
  - (ii) batch number
  - (iii) date and source of sample; the original manufacturer’s label may be helpful.
- (b) Check that the records contain the following:
  - (i) number of samples
  - (ii) types of packaging and storage conditions
  - (iii) circumstances of sampling that may include suspected quality defects.
- (c) Place seals on containers of the samples.
- (d) Hand over one-third of the samples to the representative of the inspected establishment.
- (e) Confirm in writing that samples were taken from the premises and have the confirmation countersigned by an appropriate official of the inspected establishment (see, for example, the sample receipt form in Appendix 4).



## References

1. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-first report.* Geneva, World Health Organization, 1990, Annex 2 (WHO Technical Report Series, No. 790).
2. *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials, Volume 1.* Geneva, World Health Organization, 1997.

## Appendix 3 Guidance for inspection when pharmaceutical products are suspected to be counterfeit, spurious or substandard

This section addresses specifically the situation in which the inspector suspects counterfeit, spurious or substandard pharmaceutical products to be present during an inspection. This may be during either a regular inspection or an investigation aimed at detecting such products.

### 1. Broad objective

The presence of counterfeit, substandard and spurious pharmaceutical products in the drug distribution channels may present a danger to public health, and it is imperative that suspect products are effectively and rapidly taken out of the distribution channels and quarantined. In order to facilitate the work of the inspector, the help of capable and experienced persons involved in the distribution of products should be obtained on a proactive basis to help identify such products.

### 2. Standard operating procedures

- (a) A written SOP for inspectors should be drawn up and made available to them.

This SOP should include at least the following information:

- (i) how the suspect product should be isolated to prevent its further distribution
- (ii) the size of the samples required for testing purposes
- (iii) the manner in which the samples should be taken
- (iv) the record-keeping procedure to be followed in recording the details of the action taken
- (v) the details which should be recorded on the receipt issued for the embargoed product and/or samples taken
- (vi) the type of materials which should be used for sealing samples or for embargoing or confiscating suspect products





- (vii) the names, addresses and telephone numbers of persons who should be contacted to report on the action taken
  - (viii) special precautions to be noted by the person initiating the sampling or seizure procedure, with particular reference to correct legal procedures to be followed
  - (ix) where appropriate, the manner in which the suspect product should be destroyed.
- (b) Where other persons are involved in the detection of counterfeit pharmaceutical products they shall operate on the basis of a suitable SOP. In any case of suspicion of counterfeit pharmaceutical products an inspector shall be notified immediately.

### 3. Counterfeit products

The following applies specifically to counterfeit products:

- (a) When examining a possible counterfeit pharmaceutical product the inspector shall first screen the product by looking, smelling, touching and listening to the sound of the packing and its contents. The inspector shall look for anything, in particular its labelling and packing, that makes the product look different from an original reference sample. A SOP may assist in examining the product in this way.
- (b) When the organoleptic examination does not give conclusive evidence the inspector shall have a sample tested using appropriate simple screening methods, such as the basic tests recommended by WHO or a suitable thin-layer chromatography method.
- (c) In addition to any full analytical testing, the drug regulatory authority of the country of origin stated on the label of the product may be asked to establish whether the product is counterfeit.
- (d) Proven cases of counterfeit pharmaceutical products shall be fully documented and communicated to all other inspectors, to increase their level of expertise. Information on counterfeit products shall also immediately be made available to drug regulatory authorities of other countries concerned and to WHO.

## Appendix 4 Sample receipt form

Institution/company (under inspection) .....

Address .....

Date of inspection .....

Name of representative of the inspected establishment .....





QUALITY ASSURANCE OF PHARMACEUTICALS

Name of inspector .....

Name of the drug and description of sample .....

Dosage form .....

Batch no. ....

Place sampled (warehouse, production line, packaging section, etc.) .....

No. of samples taken (tins, packets, etc.) .....

Signature  
Inspector

Signature  
Representative of the  
inspected establishment

Quality systems requirements for national good manufacturing practice inspectorates

Background	177
1. Introduction	177
2. Glossary	177
3. Administrative structure	178
4. Terms of reference	179
5. Organizational structure	179
6. Inspection personnel	181
7. Documentation	182
8. Records	183
9. Inspection procedures	184
10. Inspection facilities required	186
11. Quality manual	187
12. Confidentiality	188
13. Publications	189
14. Appeals	189
15. Internal audit and periodic review	190
16. Complaints	191
17. Recalls	191
References	192

<sup>1</sup> Ref. WHO Technical Report Series, No 902, 2002, Annex 8, pp. 101–118.



## Background

Following the provisional guidelines on the inspection of pharmaceutical manufacturers (1), the WHO Expert Committee on Specifications for Pharmaceutical Preparations acknowledged that additional guidelines concerning national inspectorates would be of value in strengthening the implementation of good manufacturing practices (GMP) (2) and enhancing mutual recognition among inspectorates.

A trend has recently become apparent in WHO Member States for non-commercial institutions, such as certification bodies, testing laboratories, etc., to introduce quality systems principles in their internal operations. The same principles are also being applied by governmental pharmaceutical inspectorates and drug control laboratories.

The Pharmaceutical Inspection Convention (PIC) has published a document (3), with the objective of adapting the standards of the International Organization for Standardization (ISO) of the 9000 series and related norms (4–8) to the activities of the GMP inspectorates of Member States. It is based on European Standard EN 45012, *General criteria for certification bodies operating quality systems certification* (9), but has been modified for this particular purpose.

## 1. Introduction

These requirements are applicable to quality systems for the operation of inspection services within competent authorities concerned with GMP inspections. It is intended that each inspection service should use these requirements as the basis for developing its own quality system.

The establishment and operation of a quality system is an essential element in the mutual recognition of national GMP inspections. The willingness to accept national inspections is significantly enhanced when it is known that the GMP inspectorate of the competent authority follows uniform procedures incorporating quality system principles. The quality system should include all the activities involved in the inspection.

## 2. Glossary

### *authorized person*

A person (among key personnel of a manufacturing establishment) responsible for the release of batches of finished products for sale (10).

### *quality audit*

An examination and assessment of all or part of a quality system with the specific purpose of improving it. A quality audit is usually conducted by outside or independent specialists or a team designated by the management for this purpose. Such audits may also be extended to suppliers and contractors (2).



## QUALITY ASSURANCE OF PHARMACEUTICALS

### *quality manual*

A handbook that describes the various elements of the system for assuring the quality of the test results generated by a laboratory (see section 11).

### *quality system*

An appropriate infrastructure, encompassing the organizational structure, procedures, processes and resources necessary to ensure adequate confidence that a product (or service) will satisfy given requirements for quality (2).

### *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 (2).

## **3. Administrative structure**

3.1 The structure, membership and operation of the GMP inspectorate should be such that impartiality is safeguarded.

3.2 The national inspection services are responsible for ensuring that the requirements of the relevant national legislation are satisfied.

3.3 All personnel employed or used by the GMP inspectorate, including outside inspectors or subcontracted personnel, should not be subject to any commercial, financial or other pressures which might affect their judgement. They should not be under the control of pharmaceutical manufacturers, and must be assessed and licensed.

3.4 The system for obtaining fees should not improperly influence the inspection procedure.

### Recommended procedure

The administrative structure, membership, operation and legal status of the GMP inspectorate should be described in the quality manual (see section 11).

The quality manual should show how all personnel working for the GMP inspectorate, including subcontracted staff or advisers, and persons serving on committees providing advice, can maintain their impartiality. The GMP inspectorate should ensure that such persons:

- (a) are not subject to any commercial, financial or other pressures which might influence their judgement;



- (b) are not improperly influenced in their inspection of pharmaceutical manufacturers or persons assessed;
- (c) have not been involved in the design or maintenance of inspected facilities by way of any consultancy service or commercial arrangement.

The remuneration of GMP inspectorate personnel engaged in inspection activities should not depend on the result of such activities or on the granting of a marketing authorization.

Only in exceptional cases may GMP inspectorates provide advisory or consultancy services. Where the GMP inspectorate does provide such services, it should develop a code of conduct or defined policy which clearly distinguishes between the process of inspection and that of providing an advisory or consultancy service to clients. This service should be of benefit to all of industry, and not solely to individual manufacturers.

## 4. Terms of reference

4.1 The functions of the GMP inspectorate should be clearly defined and should cover:

- (a) legal responsibilities;
- (b) the formulation of policies;
- (c) an overview of the implementation of its policies;
- (d) an overview of its finances;
- (e) as required, the setting-up of committees to which defined activities are delegated.

### Recommended procedure

The terms of reference, legal responsibilities and functions of the GMP inspectorate and the way in which policy guidelines are established should be documented in the quality manual.

For any committee established to advise the GMP inspectorate or the chief inspector, the following details should be included:

- (a) its role and function;
- (b) the procedure for selecting and appointing the members (the names of the chairperson, secretary and members, their current appointments and the interests, if any, which they represent on the committee, should be available);
- (c) the rules of procedure.

## 5. Organizational structure

5.1 The GMP inspectorate should have an organization that enables it to maintain the capability to perform its technical functions satisfactorily.



## QUALITY ASSURANCE OF PHARMACEUTICALS

5.2 The GMP inspectorate should have:

- (a) documentation clearly identifying its legal status;
- (b) an organizational chart showing clearly the responsibility and reporting structure of the inspectorate and, in particular, the relationship between its inspection and authorization (licensing) functions;
- (c) a description of the means by which the inspectorate obtains financial support;
- (d) a description of the relationship between the GMP inspectorate and other departments within the drug regulatory authority and other government agencies, where they operate as separate bodies.

5.3 The GMP inspectorate should have and make available a formal statement explaining how the results of inspections are taken into account in granting and maintaining authorizations (licences).

5.4 The senior management of the GMP inspectorate should make a formal commitment to the recommended principles by ensuring that the quality policy of the inspectorate is documented, relevant to the objectives, and implemented.

5.5 The responsibility, authority and reporting structure of the GMP inspectorate should be clearly defined and documented (see above) and should be supported by written job descriptions for each member of staff.

5.6 An appropriately experienced, responsible and qualified person (2) should be nominated to carry out the quality assurance function, including implementing and maintaining the quality system. This person should have direct access to senior management. If necessary, this task may be assigned to more than one person.

5.7 The GMP inspectorate should have sufficient resources at all levels to enable it to attain its objectives effectively and efficiently. Senior management should ensure that all personnel are competent to carry out their assigned duties. They should receive appropriate training that should be documented and its effectiveness assessed.

5.8 Periodic management reviews of the quality system should be conducted and documented; records of these reviews should be retained for a specified period of time.

### Recommended procedure

The above-mentioned recommendations are intended to ensure a reasonable level of transparency, both nationally and internationally.

The organizational chart, source(s) of finance, legal status of the GMP inspectorate and its relationship with the drug regulatory authority and other



government agencies should be documented in the quality manual, together with a description of the quality system.

## 6. Inspection personnel

6.1 The personnel of the GMP inspectorate should be competent to perform the functions that they undertake.

6.2 The GMP inspectorate should maintain information on the relevant qualifications, training and experience of each inspector. Records of training and experience should be kept up to date.

6.3 Personnel should have clear, documented instructions specifying their duties and responsibilities. These instructions should be kept up to date.

6.4 When work is subcontracted to an external body or use is made of experts, the inspectorate should ensure that the personnel employed meet the relevant requirements of the quality system. The liability of third party inspectors should be clearly defined in the contract or agreement.

6.5 The GMP inspectorate should possess the required personnel, expertise and other resources to perform inspections of manufacturers and wholesale distributors to determine whether they comply with the principles and guidelines of current good practices and with the relevant legislation.

6.6 The staff responsible for inspections should have appropriate qualifications, training, experience and knowledge of the inspection process. They should have the ability to make professional judgements as to the conformity of the inspected party with the requirements of good practices and the relevant legislation and be able to make an appropriate risk assessment. Knowledge of current technology is essential, including computerized systems and information technology.

6.7 The GMP inspectorate should establish a documented system for recruiting and training its personnel. The training received and the training needs of each member of staff should be regularly reviewed, and individual training records should be maintained.

### Recommended procedure

The credibility of the GMP inspection process will depend to a large degree on the technical competence and integrity of the inspectors. The quality manual should provide up-to-date details of the names, qualifications, experience and terms of reference (job description and duties to be performed) of each member of staff engaged in the GMP inspection process (see also section 10).

Formal arrangements should exist for personnel training, and details of these arrangements should be documented. Training undertaken by each member of



## QUALITY ASSURANCE OF PHARMACEUTICALS

staff engaged in GMP inspections should be documented (see also “Recommended procedure” in section 10).

A documented procedure for selecting the members of an inspection team and deciding on its size should be available. The inspection team may include a person or persons with specialist knowledge and/or experience of a particular area of technology.

If an inspection is carried out on behalf of the GMP inspectorate by an external body or person, the GMP inspectorate should ensure that the external personnel satisfy the relevant requirements contained in these recommendations.

GMP inspectors working with or advising the GMP inspectorate should:

- (a) be academically qualified in a recognized scientific/technological discipline related to pharmaceuticals (normally pharmacy, chemistry or microbiology); direct personal experience of pharmaceutical manufacture or control is not a requirement but would be considered as a valuable asset for an inspector;
- (b) have satisfactorily completed a recognized training course on auditing quality management systems;
- (c) undergo at least 10 days of training per year (e.g. courses, symposia, conferences, etc.);
- (d) have a competent working knowledge of the WHO guidelines on GMP for pharmaceutical products (2) and/or the GMP inspection procedures of the relevant national regulatory authority;
- (e) have undergone appropriate training in the current procedures and techniques of GMP inspections before conducting an inspection alone;
- (f) have the necessary personal qualities of integrity, tact and character to perform the duties of a GMP inspector.

## 7. Documentation

7.1 The GMP inspectorate should maintain a system for the control of all documentation relating to GMP inspections of manufacturers and recommendations relating to authorization holders, and should ensure that:

- (a) the current versions of the appropriate documentation are available at all relevant locations;
- (b) all revised documents or amendments to documents are correctly authorized and processed in a manner which ensures that they are introduced without delay;
- (c) superseded documents are removed from use throughout the GMP inspectorate and elsewhere in the organization and its agencies, but are retained for a defined period of time.

7.2 The GMP inspectorate should ensure that all of its activities are described in SOPs that clearly describe the responsibilities, policy and actions. These should





include, but not be limited to, training (introduction, GMP and task-related), inspections, reporting after inspections, handling of complaints, licensing (issue, suspension, revocation), certification, documentation control, planning and handling of appeals.

7.3 Proper and accessible records should be maintained of the activities carried out, including training, as well as the assessment of inspectors after training, the preparation of inspection reports, the handling of complaints, and the drawing-up of authorized checklists (where in use) and other related documents.

7.4 Reports should be prepared on all inspections performed. They should be prepared in the approved format, and signed and dated by the relevant inspector.

7.5 The documentation system should ensure that any changes to documents are made in a controlled manner and are properly authorized. There should be a means of identifying changes in individual documents.

### Recommended procedure

The following information should be included or referred to in the quality manual:

- (a) a list of all the documents used;
- (b) for each document, the name(s) or position(s) of the person(s) responsible for authorizing its issue and any subsequent amendments or changes;
- (c) a description of the system whereby relevant documents and subsequent amendments are made available at the appropriate location from the point of view of the functioning of the inspection process;
- (d) the method by which amendments and changes are made, so that documents are speedily updated, changes recorded and superseded documents promptly withdrawn and archived.

## 8. Records

8.1 The GMP inspectorate should maintain a system of records to suit its particular method of operation and circumstances. It must comply with the relevant obligations under national legislation and demonstrate that the quality system is operating satisfactorily.

8.2 Records should be available which demonstrate that all the relevant procedures have been followed in the performance of each GMP inspection, including the initial inspection, the recommendation for issue of a marketing authorization, routine inspections and corrective action.



8.3 All records should be safely stored for an adequate period, and held under conditions that guarantee their security and confidentiality, unless otherwise required by the national legislation.

### Recommended procedure

The quality manual should describe or refer to separate SOPs which describe the system adopted by the GMP inspectorate for maintaining its records. The manual should include blank specimen copies of the various checklists, certificates and reports used during the inspection process and describe the way in which these are processed, stored and archived, and/or disposed of.

The procedures for recommending to the authorization holder the issue, suspension or revocation of marketing authorizations should be described.

Documented staff instructions on security and on the use and handling of inspection reports should be identified and described in accordance with the confidentiality requirements specified in national legislation. Information as to who should have access to confidential information should be given and such access should be controlled.

Records associated with inspection activities should be retained for a minimum period of three full inspection cycles or for 6 years, whichever is the longer.

## 9. Inspection procedures

9.1 The GMP inspectorate should have the required resources (financial, human, facilities and others) and documented procedures to enable the inspection of manufacturing operations to be carried out in accordance with the requirements of the WHO guidelines on GMP (2) and/or the national GMP guidelines.

9.2 The GMP inspectorate should require the manufacturer to have documented procedures in accordance with a quality management system, and complying with the WHO guidelines on GMP (2) and/or the national GMP guidelines.

9.3 The GMP inspectorate should perform regular inspections of the manufacturing premises, procedures and quality systems of authorization holders at least once every 2 years in accordance with a written inspection programme. Written inspection reports should be prepared and sent to the national regulatory authority to keep it informed of the outcome of such inspections.

9.4 The planning of inspections of manufacturers and the assessment of compliance with the planning regarding the performance of the different types of inspections should be documented. The types of inspections should include as a minimum routine inspections, specific inspections, follow-up inspections and concise inspections.

9.5 The activity of the GMP inspectorate should be described, indicating how it relates to the system(s) for granting manufacturers' and product authorizations.



9.6 The activities relating to post-marketing surveillance and product testing should be described. The description should also cover the process of handling non-conforming products (e.g. substandard or counterfeit products).

9.7 The procedure for operations in support of a surveillance sampling programme should be documented.

9.8 The GMP inspectorate should have the documented procedures and resources to enable the inspection of manufacturing and wholesale distribution operations to be carried out in accordance with the official guidelines and national legislation. A formal inspection plan should be followed. All instructions, standards or written procedures, worksheets, checklists and reference data relevant to the work of the GMP inspectorate should be kept up to date and be readily available to staff.

9.9 A chief inspector should be appointed to coordinate inspection activities if more than one inspector is involved in an inspection. The lead inspector, who should be selected by all the participating inspectors, should normally prepare the inspection report.

9.10 Observations and/or data obtained in the course of inspections should be recorded in a timely manner to prevent loss of relevant information.

9.11 Completed inspections should be reviewed to ensure that the requirements have been met.

### Recommended procedure

The procedures covering initial inspections of new applicants for marketing authorizations and ongoing inspections of authorization holders should be documented.

Manufacturers should be inspected at least every 1 or 2 years, although new authorization holders should be inspected more frequently until inspectors are confident that the manufacturers are complying with the WHO guidelines on GMP and/or the national GMP guidelines. The frequency of inspection should not normally fall below once every 2 years as lack of continuity may give rise to a reduced awareness of current GMP or allow significant deficiencies to develop.

The time available for undertaking inspections should be adequate to enable sufficient investigations and enquiries to be made to give confidence in the findings of the inspection.

The report to the authorization holders following GMP inspections should include as a minimum:

- (a) the name and location of the manufacturing site(s);
- (b) the date(s) of the inspection(s);



## QUALITY ASSURANCE OF PHARMACEUTICALS

- (c) the reason for the inspection and the product categories and manufacturing areas inspected;
- (d) the suitability of key personnel, including the authorized person;
- (e) observations, failures to comply with the WHO guidelines on GMP and/or the national GMP guidelines, and the recommended frequency of reinspection;
- (f) a recommendation on the issue/continuation, suspension or revocation of the marketing authorization.

The GMP inspectorate should have the power, under the national or regional legislation or other arrangements, to require reinspection of a manufacturer's premises if there are changes in personnel, facilities, internal organization or scope of activity, or if analysis of a complaint or any other information indicates that the manufacturer is failing to comply with the requirements of the WHO guidelines on GMP and/or the national GMP guidelines, or with the conditions imposed by the marketing authorization.

### 10. Inspection facilities required

10.1 The inspection service should have the required facilities in terms of staff, expertise, equipment and other resources to perform inspections of manufacturers to determine compliance with the requirements of the WHO guidelines on GMP and/or the national GMP guidelines. This does not preclude the use of external resources, when necessary, provided that the requirements as described for "subcontracting" are met (see section 3.3).

10.2 If inspections are carried out on behalf of the GMP inspectorate by an external body or person, the GMP inspectorate should ensure that this body or person satisfies the requirements specified in section 3.3. A properly documented agreement covering these arrangements, including confidentiality aspects and the declaration of any conflict of interests, should be drawn up.

#### Recommended procedure

A sufficient number of competent personnel should support the GMP inspectorate, whether employed or contracted for the functions that they undertake.

The quality manual should describe the procedures for the management of the GMP inspectors and of the necessary records. A record should be kept for each individual employed to carry out GMP inspections (whether an employee or under contract), which should include the following information:

- (a) the name;
- (b) the designated area of responsibility within the declared scope of the GMP inspectorate;



- (c) the educational qualifications;
- (d) the professional qualifications, where relevant to the activities of the GMP inspectorate;
- (e) the work experience;
- (f) details of the GMP inspector training received, supported by documentary evidence of course attendance and assessment results.

Where an external body or person carries out a GMP inspection, the quality manual should describe the process adopted by the GMP inspectorate to comply with the above-mentioned requirements.

Whenever an external body or person is used to carry out any function on behalf of a GMP inspectorate, the GMP inspectorate should have documented evidence to demonstrate that the external body or person concerned is competent to do so.

Staff members authorized to carry out audits of external bodies or persons should be identified.

Documented agreements with all external bodies or persons should be available for scrutiny.

A register of all external bodies or persons employed by the GMP inspectorate should be maintained. The register should include:

- (a) the name of the external body or person;
- (b) the legal status of the external body and details of any relationship with a parent company, group of companies or any other organization of which the external body or person is part, with specific reference to possible conflicts of interest;
- (c) the names and qualifications of all personnel engaged in GMP inspection work for the GMP inspectorate.

## 11. Quality manual

11.1 The GMP inspectorate should define and document its policy and objectives for, and commitment to, quality in a quality manual. It should ensure that this policy is understood, implemented and maintained at all levels in the organization.

11.2 The information contained in the quality manual and procedures should include at least:

- (a) a quality policy statement;
- (b) a brief description of the legal status of the GMP inspectorate (see section 4.1(a));
- (c) a code of ethics and conduct relating to GMP inspection activities;
- (d) a description of the organization of the GMP inspectorate, including details of any governing board, its constitution, terms of reference and rules of procedure (see section 5.2(b));

- (e) the names, qualifications, experience and terms of reference of the senior staff and other GMP inspection personnel, both internal and external (see sections 6 and 10);
- (f) details of training arrangements for inspection personnel (see sections 6 and 10);
- (g) an organizational chart showing the responsibility and reporting structure of the inspectorate and the allocation of functions stemming from the person in charge of the GMP inspectorate (see section 5.2(b));
- (h) details of the documented procedures for inspecting manufacturers under the WHO guidelines on GMP and/or the national GMP guidelines (see section 8);
- (i) details of the documented procedures for recommendations to the authorization holder for the issue, suspension or revocation of marketing authorizations (see sections 7.2 and 8.1);
- (j) a list of any subcontractors used for GMP inspections and details of the documented procedures for assessing and monitoring their competence (see section 6);
- (k) details of appeals procedures (see section 14);
- (l) a procedure for ensuring that complaints made to the GMP inspectorate are investigated so that any shortcomings of the authorization holders are revealed (see section 16);
- (m) a list of those staff members responsible for investigating complaints and those with the authority to take remedial action (see section 16);
- (n) details of internal quality audits (see section 15);
- (o) details of testing of samples (see sections 9.6–9.8);
- (p) the control of non-conforming products (see section 9.6).

### Recommended procedure

In order to keep the quality manual brief, reference may be made to other documents and/or procedures contained in other manuals.

## 12. Confidentiality

12.1 The GMP inspectorate should have adequate arrangements to ensure confidentiality of the information obtained in the course of its inspection activities at all levels of its organization, including committees.

12.2 The exchange of inspection reports between countries should be described. The format and content of reports should be specified.



### Recommended procedure

The quality manual should describe how the GMP inspectorate discharges its responsibility for ensuring that all communications between itself and the companies inspected are kept confidential. The following are necessary:

- (a) instructions to personnel on confidentiality;
- (b) a written undertaking by all personnel not to divulge to third parties any information gained about any business affairs of clients;
- (c) the inclusion of provisions in all subcontracts to maintain confidentiality;
- (d) provisions to ensure the physical security of all documents and records relating to inspection activities.

## 13. Publications

13.1 The GMP inspectorate should produce and update, as necessary, a list of authorization holders, together with an outline of the scope of the marketing authorization issued to each manufacturer. The extent to which this list will be distributed should be specified.

13.2 An outline of the inspection and marketing authorization system should be available in published form.

13.3 Other publications, such as GMP guidelines and other guidelines and information brochures, should be available to industry and other interested parties, as appropriate.

### Recommended procedure

The quality manual should list the publications issued by the authorization holder and GMP inspectorate. The following information should also be provided:

- (a) the name of the person responsible for compiling and updating each publication;
- (b) the frequency with which each publication is updated;
- (c) how the publications are distributed and to whom;
- (d) the procedure for issuing amendments.

## 14. Appeals

14.1 The GMP inspectorate should have procedures for the consideration of appeals against its decisions.



### Recommended procedure

Appeals procedures should be established by the GMP inspectorate and should include:

- (a) the method by which an appeal may be lodged;
- (b) the method by which an impartial appeals panel, independent of the activity under review, is selected;
- (c) the names and positions of the members of the GMP inspectorate to whom appeals are referred, and the procedure for handling them;
- (d) a register of all appeals and their outcome.

## 15. Internal audit and periodic review

15.1 The GMP inspectorate should implement a system of planned and documented internal audits and periodic reviews of its compliance with the criteria of these guidelines.

15.2 There should be procedures for corrective and preventive action whenever faults are detected in the quality system, or in the performance of inspections and the general performance of the inspection service.

15.3 The management of the inspectorate should periodically review the quality system for its continuing suitability and effectiveness.

15.4 Inspectors should be evaluated before being allowed to perform inspections. Periodic reviews should also be undertaken to examine the performance of individual inspectors in order to ensure consistency among them, and in the operations and procedures of the GMP inspectorate.

15.5 A record of all audits and reviews should be kept and should include the findings, conclusions, recommendations and follow-up action. These records should be retained for a specified period of time.

### Recommended procedure

Internal periodic review procedures should be documented. The review procedure should include internal audits by staff competent to ensure that all formulated procedures are adhered to. Based on the results of these audits, management must ensure that the GMP inspection system remains effective and that inspections conducted by different inspectors arrive at similar conclusions when the same operation is inspected under the same conditions.

Internal audit procedures should state:

- (a) the names or positions of staff members authorized to conduct internal audits;





- (b) what is to be examined and how often (a schedule for the examination of the whole organization over a given period should be drawn up);
- (c) how the audit will be conducted;
- (d) to whom the results will be reported;
- (e) who will initiate any corrective action.

Management reviews should take account of the results of internal audits and should include:

- (a) consideration of the overall operation of the GMP inspectorate;
- (b) uncovering defects or irregularities in the operation of the GMP inspection system;
- (c) ensuring that action has been taken to effectively correct defects revealed in previous reviews and audits.

Periodic audit by an experienced person or persons from another national regulatory authority is a useful means of providing an independent review of the GMP inspectorate's operations and procedures.

## 16. Complaints

16.1 The GMP inspectorate should have documented procedures for dealing with complaints arising from its activities.

16.2 A record should be maintained of all complaints received and the actions taken by the GMP inspectorate. These records should be retained for a specified period of time.

### Recommended procedure

The GMP inspectorate should require each authorization holder to keep a record of all complaints received, as well as remedial actions relating to the manufacturing activities and products covered by the marketing authorization.

The GMP inspectorate should have a procedure for recording and investigating complaints received about its inspection activities. The procedure should include a list of those staff members responsible for investigating complaints and those with the authority to take remedial action.

## 17. Recalls

17.1 The GMP inspectorate should have a documented procedure for dealing with recalls and withdrawals of products from the market.

17.2 Records should be maintained of all recalls and withdrawals registered and dealt with by the inspectorate.



## References

1. Provisional guidelines on the inspection of pharmaceutical manufacturers. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report*. Geneva, World Health Organization, 1992, Annex 2 (WHO Technical Report Series, No. 823).
2. *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Vol. 2. Good manufacturing practices and inspection*. Geneva, World Health Organization, 1999.
3. *Recommendations on quality system requirements for GMP inspectorates of PIC Contracting States*. Geneva, Pharmaceutical Inspection Convention, 1994 (unpublished document PH/7/94; available from EFTA Secretariat, 9–11 rue de Varembe, 1211 Geneva 20, Switzerland).
4. *Quality management and quality assurance standards — guidelines for selection and use. International Standard ISO 9000*. Geneva, International Organization for Standardization, 1990.
5. *Quality systems — model for quality assurance in design/development, production, installation and servicing. International Standard ISO 9001*. Geneva, International Organization for Standardization, 1994.
6. *Quality systems — model for quality assurance in production, installation and servicing. International Standard ISO 9002*. Geneva, International Organization for Standardization, 1994.
7. *Quality systems — model for quality assurance in final inspection and test. International Standard ISO 9003*. Geneva, International Organization for Standardization, 1994.
8. *Quality management and quality system elements — guidelines. International Standard ISO 9004*. Geneva, International Organization for Standardization, 1990.
9. *General criteria for certification bodies operating quality systems certification. European Standard EN 45012*. Brussels, European Committee for Standardization, 1989 (available from CEN Central Secretariat, 36 rue de Stassart, B-1050 Brussels, Belgium).
10. Good manufacturing practices: authorized person — role, functions and training. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fifth report*. Geneva, World Health Organization, 1999, Annex 4 (WHO Technical Report Series, No. 885).



## Guidance on Good Manufacturing Practices (GMP): inspection report<sup>1</sup>

When a site at which pharmaceutical products are manufactured is inspected, the inspector(s) responsible must draw up a report containing the items listed below. Where relevant, the appropriate section of the WHO GMP (Annex 4) is indicated.

### A. Manufacturer

- (a) Name of inspected manufacturer.
- (b) Address of inspected manufacturer (including telephone, fax, email and 24-hour telephone numbers).
- (c) Address of manufacturing site if different from that given above.
- (d) Site number (e.g. site master file or number allocated by the responsible authority).
- (e) Manufacturing licence number, if applicable.
- (f) Activities.
- (g) Pharmaceutical products manufactured.
- (h) Key personnel.
- (i) Key persons met.

### B. Inspection details

- (a) Date(s) of inspection(s).
- (b) Previous inspection date.
- (c) Type of inspection.
- (d) Scope of inspection.
- (e) The regulatory authority.
- (f) GMP guidelines used for assessing compliance.
- (g) For foreign inspections state whether, the national regulatory authority (NRA) of the country where the inspection took place was informed and whether it took part in the inspection.
- (h) Brief report of inspection activities undertaken.
- (i) Samples taken and results obtained.
- (j) Assessment of the site master file.
- (k) GMP-related recalls from the market of any product in the last 2 years.

### C. Inspector(s)

- (a) Name(s) of inspector(s) and accompanying experts.

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<sup>1</sup> Ref. WHO Technical Report Series No 908 2003 Annex 6, pp. 94–98



## D. Introduction

- (a) Brief summary of the manufacturing activities.
- (b) Other manufacturing activities carried out on the site (e.g. manufacture of cosmetics, research and development).
- (c) Use of outside scientific, analytical, or other technical assistance in manufacture and quality control.
- (d) Brief description of the quality management system of the firm responsible for manufacture. Reference can be made to a site master file if one is available.

## E. Observations

*The observations made during the inspection that are considered to be non-compliant with GMP should be listed. Where positive observations are included in the report, clear distinction should be made between “positive” and “non-compliant”. Non-compliant observations can be classified, e.g. as “critical”, “major” and “minor” if the Member State concerned has defined these terms. The date by which corrective action and completion are requested in accordance with the policy of the national regulatory authority should be given.*

### E.1 Quality assurance (see WHO GMP, section 1)

- (a) Quality system and documented quality policy of the manufacturer, e.g. as described in the quality manual.

### E.2 Organization and personnel (see WHO GMP, section 9)

- (a) Organizational chart showing the arrangements for quality assurance, including production and quality control.
- (b) Qualifications, experience and responsibilities of key personnel.
- (c) Outline of arrangements for basic and in-service training and method of keeping records.
- (d) Health requirements for personnel engaged in production.
- (e) Personnel hygiene requirements, including clothing.

### E.3 Premises (see WHO GMP, section 12)

- (a) Manufacturing areas (design, location etc.) used e.g. for storage and manufacturing (e.g. weighing, production, packaging) and flow of personnel and material.
- (b) Special areas for the handling of highly toxic, hazardous and sensitizing materials.
- (c) Nature of construction and finishes.



- (d) Systems such as drainage, ventilation, air conditioning, and supply of steam and gas. Detailed description of critical areas with potential risks of contamination and cross-contamination.
- (e) Classification of the rooms used for the manufacture of products, including clean rooms.
- (f) Water systems.
- (g) Planned preventative maintenance programme.
- (h) Qualification of premises and systems as appropriate.

#### E.4 Equipment (see WHO GMP, section 13)

- (a) Design, location and adaptation of equipment used in production and control laboratories.
- (b) Planned preventative maintenance programmes for equipment and records.
- (c) Qualification and calibration, including records.

#### E.5 Materials (see WHO GMP, section 14)

- (a) Sourcing of materials.
- (b) Control, storage and handling of materials, including:
  - starting materials;
  - packaging materials;
  - intermediate and bulk products;
  - finished products;
  - returned and rejected materials;
  - reagents and culture media;
  - reference standards;
  - waste material.

#### E.6 Good practices in production (see WHO GMP, section 16)

- (a) Transport, handling and use of starting materials, packaging materials, and bulk and finished products.
- (b) Production operations and important parameters (e.g. sampling, quarantine, weighing, process operations and conditions, acceptance limits).
- (c) Validation (e.g. process).
- (d) Change control and deviation reporting.

#### E.7 Quality control (see WHO GMP, section 17)

- (a) Activities of quality control (including quarantine control, sampling, chemical and microbial analysis).
- (b) Organization and personnel.
- (c) Premises.



## QUALITY ASSURANCE OF PHARMACEUTICALS

- (d) Equipment and instrumentation.
- (e) Materials.
- (f) Documentation (e.g. specifications, procedures, reports, records).

### E.8 Sanitation and hygiene (see WHO GMP, section 3)

- (a) Procedures for sanitation and/or cleaning (e.g. of premises and equipment) and records.
- (b) Personal hygiene.

### E.9 Validation (see WHO GMP, section 4)

- (a) Validation master plan.
- (b) Validation and qualification protocols and reports for qualification and validation (e.g. of premises, systems, equipment, process, computer, cleaning, analytical methods).
- (c) Stages of validation.
- (d) Types of validation.

### E.10 Documentation (see WHO GMP, section 15)

- (a) Documentation (e.g. specifications, procedures, records, protocols, reports).
- (b) Preparation, revision and distribution of documentation.
- (c) Reports on production, quality control (including environmental control), engineering and other relevant areas.

### E.11 Complaints (see WHO GMP, section 5)

- (a) Procedure, records and investigation.

### E.12 Product recalls (see WHO GMP, section 6)

- (a) Procedure, records and investigation.

### E.13 Contract production and analysis (see WHO GMP, section 7)

- (a) Responsibilities of contract giver.
- (b) Responsibilities of contract acceptor.
- (c) Contract (containing clearly defined responsibilities).
- (d) GMP compliance of the contract acceptor (initial assessment and continued compliance audited at regular intervals).



## E.14 Self-inspection and quality audits (see WHO GMP, section 8)

- (a) Procedure, programme and compliance.
- (b) Items for self-inspection.
- (c) Self-inspection team.
- (d) Frequency of self-inspection.
- (e) Self-inspection report.
- (f) Follow-up action.
- (g) Quality audit.
- (h) Suppliers' audits.

## F. Summary

Brief summary of the findings, and recommendations (where applicable).

## G. Conclusions

A statement regarding the GMP status.

Name: \_\_\_\_\_ Signature: \_\_\_\_\_ Date: \_\_\_\_\_

## Model certificate of Good Manufacturing Practices<sup>1</sup>

A model certificate of Good Manufacturing Practices (GMP) for a manufacturing site is suggested (see below). This is not part of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce but is intended to serve in situations where a specific GMP certificate is requested by importers, exporters, procurement agencies and regulatory authorities. It is suggested that the certificate should remain valid for a period of 2 years from the date of issue, but not exceeding 3 years after the inspection was carried out.

It is recommended that, where possible, GMP certificates should have, e.g. security seals, watermarks or holograms, to help prevent counterfeiting, tampering and other fraudulent activities.

## Letterhead of regulatory authority

### Model Certificate of Good Manufacturing Practices

This one-page certificate conforms to the format recommended by the World Health Organization (general instructions and explanatory notes attached).<sup>2</sup>

<sup>1</sup> Ref. WHO Technical Report Series No 908, 2003, Annex 5, pp. 90–93

<sup>2</sup> This model certificate for GMP is not part of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce.



QUALITY ASSURANCE OF PHARMACEUTICALS

Certificate No: \_\_\_\_\_

On the basis of the inspection carried out on \_\_\_\_ [date] \_\_\_\_ we certify that the site indicated on this certificate complies with Good Manufacturing Practices for the dosage forms, categories and activities listed in Table 1.

1. Name and address of site:

\_\_\_\_\_

2. Manufacturer's licence number:

\_\_\_\_\_

3. Table 1:

Dosage form(s)	Category(ies)	Activity(ies)

The responsibility for the quality of the individual batches of the pharmaceutical products manufactured through this process lies with the manufacturer.

This certificate remains valid until \_\_\_\_ [date] \_\_\_\_ It becomes invalid if the activities and/or categories certified herewith are changed or if the site is no longer considered to be in compliance with GMP.

Address of certifying authority:

\_\_\_\_\_

Name and function of responsible person:

\_\_\_\_\_

Email: \_\_\_\_\_ Telephone no.: \_\_\_\_\_ Fax no.: \_\_\_\_\_

Signature:

Stamp and date:

\_\_\_\_\_

Explanatory notes

- (1) This certificate, which is in the format recommended by WHO, certifies the status of the Site listed in point 1 of the certificate.
- (2) The certification number should be traceable within the regulatory authority issuing the certificate.





(3) Where the regulatory authority issues a licence for the site this number should be specified. Record “not applicable” in case where there is no legal framework for the issuing of a licence.

(4) Table 1

List the dosage forms, starting materials, categories and activities. Examples give below.

*Example 1*

<i>Pharmaceutical Product(s)<sup>1</sup></i>	<i>Category(ies)</i>	<i>Activity(ies)</i>
<i>Dosage form(s):</i>		
Tablets	Cytotoxic	Packaging
	Hormone	Production, packaging, quality control
	Penicillin	Repackaging and labelling
Injectables	Cefalosporin	Aseptic preparation, packaging, labelling

*Example 2*

<i>Pharmaceutical Product(s)<sup>1</sup></i>	<i>Category(ies)</i>	<i>Activity(ies)</i>
<i>Starting material(s):<sup>2</sup></i>		
Paracetamol	Analgesic	Synthesis, purification, packing, labelling

<sup>1</sup> Pharmaceutical Products: 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.

<sup>2</sup> Starting Materials: Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials.



# 5.

## Hazard and risk analysis in pharmaceutical products<sup>1</sup>

Application of Hazard Analysis and Critical Control Point (HACCP) methodology to pharmaceuticals

### 1. Introduction

Traditionally, the Hazard Analysis and Critical Control Point (HACCP) methodology has been considered to be a food safety management system. It aims to prevent known hazards and to reduce the risks that they will occur at specific points in the food chain. The same principles are also increasingly being applied, in other industries, such as the car industry, aviation and the chemical industry.

This text provides general guidance on the use of the HACCP system to ensure the quality of pharmaceuticals, while recognizing that the details of its application may vary depending on the circumstances (see Appendix 1). It does not provide detailed information on major hazards.

Hazards affecting quality are controlled to a certain extent through the validation of critical operations and processes in the manufacture of finished pharmaceutical products in accordance with Good Manufacturing Practices (GMP). However, GMP do not cover the safety of the personnel engaged in manufacture, while both aspects are covered by HACCP.

Procedures, including GMP, address operational conditions and provide the basis for HACCP. HACCP is a systematic method for the identification, assessment and control of safety hazards. Such hazards are defined as biological, chemical, or physical agents or operations that are reasonably likely to cause illness or injury if not controlled. In the manufacture of pharmaceuticals,<sup>2</sup> these may include the manufacture of certain antibiotics, hormones, cytotoxic substances or other highly active pharmaceuticals, together with operations such as fluid-bed drying, granulation is an example of hazard unit operations. The use of

<sup>1</sup> Ref. WHO Technical Report Series, No 908, 2003, Annex 7, pp. 99–112

<sup>2</sup> Safety hazards are common in the manufacture of active pharmaceutical ingredients; e.g., dangerous chemical conversions such as catalytic hydrogenation or nitration, or handling reactions with extremely hazardous chemicals such as phosgene or methyl-isocyanate require special precaution and control measures.



inflammable solvents (solutions) and certain laboratory operations may also constitute hazards.

The following elements of the HACCP methodology are integral parts of the validation master file:

- development of a flow diagram of the process;
- verification of the flow diagram on site.

In addition, HACCP will extend this concept to include an analysis of the critical quality variables as well as the assessment of hazards affecting the safety of workers and environmental pollution hazards directly related to the process (in particular in open systems) concerned.

GMP for pharmaceutical products require the validation of critical processes as well as of changes in the manufacturing process which may affect the quality of the final product. Experience shows that most manufacturing processes contain steps that are “critical” from the point of view of variations in final product quality.

HACCP should not be confused with validation since its approach is broader; it thereby helps to identify matters on which validation should concentrate. It is science-based and systematic, and identifies specific hazards and measures for their control, as well as providing information on environmental protection and labour safety. HACCP is a tool to assess hazards and establish, control systems that focus on prevention rather than relying on corrective action based on end-product testing. All HACCP systems are capable of accommodating changes, such as advances in equipment design and processing procedures or technological developments.

HACCP should not replace GMP; however, its application may be used as a first step towards GMP.

In countries where appropriate regulations exist and are enforced, compliance with GMP (including validation), drug regulatory activities and inspections provide good assurance that risks are largely controlled. In countries where control is less effective, however, patients may be put at risk through the production of drugs of inadequate quality. The assessment of individual risks related to specific products and starting materials, and the recognition of hazards at specific stages of production or distribution should permit regulatory authorities to improve drug control by increasing the effectiveness of their activities within the limits of the available resources.

The present guidelines are aimed at assisting industry to develop and implement effective HACCP plans covering activities such as research and development, sourcing of materials, manufacturing, packaging, testing and distribution.

## 2. Links with other programmes

In each stage of the manufacture and supply of pharmaceuticals, the necessary conditions should be provided and met to protect the pharmaceuticals concerned.



## QUALITY ASSURANCE OF PHARMACEUTICALS

This has traditionally been accomplished through the application of Good Clinical Practice (GCP), Good Laboratory Practice (GLP), GMP and other guidelines, which are considered to be essential to the development and implementation of effective HACCP plans. HACCP plans are focused on hazards, the overall objective being to ensure that pharmaceuticals are safe for use. The existence and effectiveness of GCP, GLP and GMP should be assessed when drawing up HACCP plans.

### 3. Definitions

The following definitions apply to the terms as used in these guidelines. They may have different meanings in other contexts.

*control (verb)*

The taking of all necessary actions to ensure and maintain compliance with the criteria established in the HACCP plan.

*control (noun)*

The state wherein correct procedures are being followed and criteria are being met.

*control measure*

Any action and activity that can be used to prevent or eliminate a pharmaceutical quality hazard or reduce it to an acceptable level.

*corrective action*

Any action to be taken when the results of monitoring at the CCP (see below) indicate a loss of control.

*critical control point (CCP)*

A step at which control can be applied and is essential to prevent or eliminate a pharmaceutical quality hazard or reduce it to an acceptable level.

*critical limit*

A criterion which separates acceptability from unacceptability.

*deviation*

Failure to meet a critical limit.

*flow diagram*

A systematic representation of the sequence of steps or operations used in the production, control and distribution of a particular pharmaceutical.



*HACCP plan*

A document prepared in accordance with the principles of HACCP to ensure the control of hazards which are significant for pharmaceutical quality in the production and supply chain.

*hazard*

Any circumstance in the production, control and distribution of a pharmaceutical which can cause an adverse health effect.

*hazard analysis*

The process of collecting and evaluating information on hazards which should be addressed in the HACCP plan.

*monitor*

The act of conducting a planned sequence of observations or measurements of control parameters to assess whether a CCP is under control.

*pharmaceuticals*

All products related to pharmacy, including starting materials (active pharmaceutical ingredients and excipients), finished dosage forms, and biological and other specific products.

*validation*

The collection and evaluation of data, beginning at the process development stage and continuing through the production phase, which ensure that the manufacturing processes — including equipment, buildings, personnel and materials — are capable of achieving the intended results on a consistent and continuous basis. Validation is the establishment of documented evidence that a system does what it is supposed to do.

*verification*

The application of methods, procedures, tests and other evaluations, in addition to monitoring, to determine compliance with the HACCP plan.

## 4. Principles

The HACCP system is based on seven principles. In applying these principles, 12 stages are recommended and are discussed in section 7. Some stages are linked to specific principles while others serve as an introduction to the concept.

The seven principles are:

1. Conduct a hazard analysis.
2. Determine the critical control points (CCPs).
3. Establish target levels and critical limit(s).



4. Establish a system to monitor the CCPs.
5. Establish the corrective action to be taken when monitoring indicates that a particular CCP is not under control.
6. Establish procedures to verify that the HACCP system is working effectively.
7. Establish documentation concerning all procedures and keep records appropriate to these principles and their application.

## 5. Guidelines for the application of the HACCP system

The following guidelines will be found useful in applying the HACCP system:

- Before HACCP is applied to any sector, that sector should be operating in accordance with the principles of good practices and the relevant legislation.
- Management commitment is necessary if an effective HACCP system is to be implemented.
- HACCP should be applied to each specific operation separately.
- CCPs identified in any given example in any reference document (including GMP guidelines) may not be the only ones identified for a specific application or may be of a different nature.
- The HACCP application should be reviewed and necessary changes made when any modification is made in the product or process, or in any step.
- It is important, when applying HACCP, to take into account the nature and size of the operation.
- There should be a HACCP plan. The format of such plans may vary, but they should preferably be specific to a particular product, process or operation. Generic HACCP plans can serve as useful guides in the development of product and process HACCP plans; however, it is essential that the unique conditions within each facility are considered during the development of all components of the HACCP plan.

## 6. Training and education

As HACCP is a relatively new concept in the pharmaceutical industry, training of personnel in industry, government and universities in HACCP principles and applications is essential for its effective implementation.

In developing specific training to support a HACCP plan, working instructions and procedures should be drawn up which define the tasks of the operating personnel to be stationed at each critical control point. Specific training should be provided in the tasks of employees monitoring each CCP.

Cooperation between producers, traders and responsible authorities is of vital importance. Opportunities should be provided for the joint training of industrial staff and the control authorities to encourage and maintain a continuous dialogue and create a climate of understanding in the practical application of HACCP.



The success of a HACCP system depends on educating and training management and employees in the importance of their role in producing safe pharmaceuticals. Information should also be provided on the control of hazards at all stages of production and supply.

Employees must understand what HACCP is, learn the skills necessary to make it function properly, and must also be given the materials and equipment necessary to control the CCPs.

## 7. Application

The application of HACCP principles consists of the following 12 stages, as identified in the logic sequence for application of HACCP.

### 7.1 Assemble a HACCP team

The pharmaceutical manufacturer should assure that product-specific knowledge and expertise are available for the development of an effective HACCP plan. This may be best accomplished by assembling a multidisciplinary team. Team members should therefore represent all the relevant disciplines, such as research and development, production, quality control, quality assurance, microbiology, engineering and distribution or others as applicable.

Team members should have specific knowledge and expertise regarding the product and process. Where such expertise is not available on site, expert advice should be obtained from other sources.

Team members should be able to:

- (a) conduct a hazard analysis;
- (b) identify potential hazards;
- (c) identify hazards which should be controlled;
- (d) recommend controls and critical limits;
- (e) devise procedures for monitoring and verification;
- (f) recommend appropriate corrective action where deviations occur;
- (g) verify the HACCP plan.

The scope of the HACCP plan should be defined. The scope should describe the segment of the process involved and the classes of hazards to be addressed should be identified.

### 7.2 Describe the product and process

A full description of the product and the process should be drawn up, including relevant quality information such as the composition, physical/chemical properties, structure, pH, temperatures, method of cleaning, bactericidal/bacteriostatic treatments (e.g. heat-treatment), drying, screening, mixing, blending, packaging,



and the storage conditions. The method of distribution and transport should also be described, especially where products are thermolabile.

### 7.3 Identify the intended use

The intended use should be based on the expected uses of the product by the end user or consumer. In specific cases, vulnerable population groups, e.g. geriatric patients, infants and immunocompromised patients, may have to be considered.

### 7.4 Construct a flow diagram

The flow diagram should be constructed by the HACCP team, and should cover all operations and decisions in a process.

When applying HACCP to a given operation, the steps preceding and following that operation should also be considered.

A block-type diagram may be sufficiently descriptive.

### 7.5 On-site confirmation of flow diagram

The HACCP team should confirm the processing operation against the flow diagram during all stages and hours of operation. Amendments to the flow diagram may be made where appropriate, and should be documented.

### 7.6 List all potential hazards associated with each step, conduct a hazard analysis, and consider any measures to control identified hazards (Principle 1)

When hazard analysis is conducted, safety concerns must be distinguished from quality concerns.

The HACCP team should list all the hazards that may be reasonably expected to occur at each step from production, testing and distribution up to the point of use. It should then conduct a hazard analysis to identify for the HACCP plan which hazards are of such a nature that their elimination or reduction to acceptable levels is essential.

A thorough hazard analysis is required to ensure an effective control point. A two-stage hazard analysis is recommended. During the first stage, the team should review the materials, activities, equipment, storage, distribution and intended use of the product. A list of the potential hazards (biological, chemical and physical) which may be introduced, increased or controlled in each step should be drawn up.

In the hazard analysis, the following should be included wherever possible:

- the probable occurrence of hazards and the severity of their adverse health effects;





- the qualitative and/or quantitative evaluation of the presence of hazards;
- the survival or multiplication of microorganisms of concern;
- the production or persistence in drugs of toxins, chemicals or physical agents;
- the conditions leading to the above.

During the second stage, a hazard evaluation should be conducted, i.e. the severity of the potential hazards and the probability of their occurrence should be estimated.

The team should then decide which potential hazards should be addressed in the HACCP plan, and what control measures, if any, exist that can be applied for each hazard. More than one control measure may be required to control a specific hazard(s) and more than one hazard may be controlled by a specified control measure.

Potential hazards in relation to at least the following should be considered:

- materials and ingredients;
- physical characteristics and composition of the product;
- processing procedures;
- microbial limits, where applicable;
- premises;
- equipment;
- packaging;
- sanitation and hygiene;
- personnel;
- risk of explosions;
- mix-ups.

Common examples of failures are given in Appendix 2.

### 7.7 Determine critical control points (Principle 2)

A CCP in the HACCP system can be more easily determined by the use of a decision-tree, which facilitates a logical approach. The way that a decision-tree is used will depend on the operation concerned, e.g. production, packing, reprocessing, storage, distribution. Training in the use of decision-trees should be given.

If a hazard has been identified at a step where control is necessary for safety, and no control measure exists at that step, or any other, the product or process should be modified at that step, or at an earlier or later stage, to include such a control measure.

### 7.8 Establish critical limits for each CCP (Principle 3)

Critical limits must be specified and verified, if possible, for each critical control point. More than one critical limit may sometimes be elaborated at a particular





step. The criteria used often include measurements of temperature, time, moisture level, pH, and sensory parameters, such as visual appearance and texture. Critical limits should be scientifically based.

### 7.9 Establish a monitoring system for each CCP (Principle 4)

Monitoring is the scheduled measurement or observation of a CCP relative to its critical limits. Monitoring should be recorded.

The monitoring procedures used must be able to detect loss of control at the CCP, and this information should ideally be available in time to make adjustments to ensure control of the process and prevent violations of the critical limits. Where possible, process adjustments should be made when monitoring results indicate a trend towards loss of control at a CCP. These adjustments should be made before a deviation occurs.

Data derived from monitoring must be evaluated by a designated person with the knowledge and authority to carry out corrective actions when indicated.

If monitoring is not continuous, the amount or frequency of monitoring must be sufficient to guarantee that the CCP is under control.

Most monitoring procedures for CCPs will need to be done rapidly because they relate to on-line processes and there will not be time for lengthy analytical testing. For this reason, physical and chemical measurements are often preferred to microbiological tests because they can be done rapidly and can often indicate the microbiological control of the product.

The personnel conducting the monitoring of CCPs and control measures should be engaged in production (e.g. line supervisors, maintenance staff) and, where appropriate, staff from quality control. They should be trained in monitoring procedures.

Where continuous monitoring is possible, a reliable monitoring procedure and frequency should be identified. Statistically designed data collection or sampling systems should then be used.

All records and documents associated with monitoring CCPs must be signed and dated by the person(s) carrying out the monitoring and by a responsible reviewing official(s) of the company.

### 7.10 Establish corrective actions (Principle 5)

Specific corrective actions should be developed for each CCP in the HACCP system in order to deal with deviations when they occur. These actions should ensure that the CCP is brought under control. Corrective actions should include at least the following:

- (a) determination and correction of the cause of non-compliance;
- (b) determination of the disposition of the non-compliant product;
- (c) recording of the corrective actions that have been taken.



Specific corrective actions should be developed in advance for each CCP and included in the HACCP plan. As a minimum, this plan should specify what is to be done when a deviation occurs, who is responsible for implementing the corrective actions, and that a record will be kept and maintained of the actions taken. Individuals who have a thorough understanding of the process, product and HACCP plan should be assigned the responsibility for the oversight of corrective actions.

As appropriate, experts may be consulted to review the information available and to assist in determining the disposition of non-compliant product. Actions taken must also include the proper disposition of the affected product.

Deviation and product disposition procedures must be documented in the HACCP records.

### 7.11 Establish verification procedures (Principle 6)

Procedures should be established for verification.

Verification and auditing methods, procedures and tests, including random sampling and analysis, can be used to determine whether the HACCP system is working correctly. The frequency of verification should be sufficient to confirm the proper functioning of the HACCP system.

Examples of verification activities include:

- review of the HACCP system and its records;
- review of deviations and product dispositions;
- confirmation that CCPs are kept under control.

Initial verification of the HACCP plan is necessary to determine whether it is scientifically and technically sound, that all hazards have been identified, and that, if the HACCP plan is properly implemented, these hazards will be effectively controlled.

Information reviewed to verify the HACCP plan should include:

- (a) expert advice and scientific studies;
- (b) in-plant observations, measurements and evaluations. For example, verification of the moist heat sterilization process for sterile injectables should include the scientific justification of the heating times, pressure and temperatures needed to obtain an appropriate destruction of pathogenic microorganisms (i.e. enteric pathogens) and studies to confirm that the sterilization conditions ensure that the whole load is kept at the required temperature for the time required.

Subsequent verifications should be performed and documented by a HACCP team or an independent expert, as needed. For example, verifications may be conducted when there is an unexplained system failure, a significant change in product, process or packaging occurs, or new hazards are recognized.



## QUALITY ASSURANCE OF PHARMACEUTICALS

In addition, a periodic comprehensive evaluation of the HACCP system by an unbiased, independent third party is useful. This should include a technical evaluation of the hazard analysis and each element of the HACCP plan as well as an on-site review of all flow diagrams and appropriate records of the operation of the plan. Such a comprehensive verification is independent of other verification procedures and must be performed in order to ensure that the HACCP plan is resulting in the control of the hazards. If the results of the comprehensive verification identify deficiencies, the HACCP team should modify the HACCP plan as necessary.

Individuals doing verification should have appropriate technical expertise to perform this function.

Where possible, verification should include actions to confirm the efficacy of all elements of the HACCP plan.

### 7.12 Establish documentation and record keeping (Principle 7)

Efficient and accurate documentation and record keeping are essential to the application of a HACCP system and should be appropriate to the nature and size of the operation.

Examples of activities for which documentation is required include:

- hazard analysis;
- CCP determination;
- HACCP plan;
- critical limit determination.

Examples of activities for which records are required include:

- CCP monitoring activities;
- process steps;
- associated hazards;
- critical limits;
- verification procedures and schedule;
- deviations;
- associated corrective actions;
- modifications to the HACCP system.

## **Appendix 1** **Illustrative examples of major industrial hazards that may form part of a HACCP plan**

The increasing use of hazardous chemicals in industry and trade further influences the quality and safety of processes and the personnel responsible for production. It is important that both on-site and off-site safety should be considered in all projects involving the storage and use of such chemicals.



This Appendix is intended only as a reminder of the major hazards that may be associated with the production, control and distribution of pharmaceuticals. Other relevant literature should be consulted, depending on the type of pharmaceuticals concerned (e.g. active pharmaceutical ingredients, vaccines).

### **1. Explosions and fires**

Explosions can cause damage to buildings, injuries to personnel and hazards to products. Types of explosions that should be considered include detonations, gas and dust explosions, and confined and unconfined vapour-cloud explosions. Because of the possibility of explosions and fires, industry is required to control operations to prevent such hazards. An appropriate hazard-control system should therefore be in place at each site where such hazards are identified.

### **2. Workers' safety**

### **3. External environment**

- 3.1 Hazardous waste
- 3.2 Spillage

## **Appendix 2 Examples of common failures**

Common failures should be identified and suitable control measures implemented.

### **1. Component failures**

Causes of such failures include bad design, pressure, corrosive media, high temperatures, mechanical failure of pumps, blowers and stirrers, failure of control systems, such as sensors, failure of welds and flanges, and failure of safety systems (e.g. valves).

### **2. Deviations from normal operating conditions**

Deviations from normal operating conditions include failures in the monitoring of crucial process parameters (e.g. pressure, temperature), failures in utilities such as steam, cooling, electricity and compressed air, failures in shut-down and start-up procedures, and formation of by-products, residues and impurities.





### **3. Human and organizational errors**

A wide variety of errors can be made by operating personnel. Common errors include operator error, pressing wrong buttons, disconnecting alarms, mix-ups of materials, communication errors, and incorrect maintenance and repairs.

### **4. Natural forces**

External impacts may be caused by natural forces such as wind, water, sunlight and lightning.

## **Bibliography**

HACCP: Introducing the Hazard Analysis and Critical Control Point System. Geneva, World Health Organization, 1997 (document member WHO/FSF/FOS/97.2).

*Major hazard control. A practical manual. An ILO contribution to the International Programme on Chemical Safety of UNEP, ILO, WHO (IPCS).* Geneva, International Labour Organization.

*Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Volume 1.* Geneva, World Health Organization, 1997.

*Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Volume 2: good manufacturing practices and inspection.* Geneva, World Health Organization, 1999.



# Subject index